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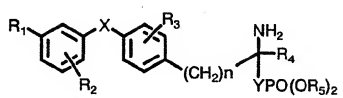
(54) **AMINOPHOSPHONIC ACID DERIVATIVES, ADDITION SALTS THEREOF AND S1P RECEPTOR MODULATORS**

(57) Aminophosphonic acid derivatives (e.g., 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentylphosphonate monoester) are represented by the following general formula (1):



(1)

and act as effective S1P receptor modulators while posing less side effects.

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Description

TECHNICAL FIELD

[0001] The present invention relates to aminophosphonic acid derivatives, salts and hydrates thereof that are useful as modulators of sphingosine-1-phosphate (S1P) receptor.

BACKGROUND ART

[0002]

Patent Article 1	WO pamphlet 0198301
Patent Article 2	WO pamphlet 03020313
Patent Article 3	WO pamphlet 02092068
Patent Article 4	WO pamphlet 0218395
Patent Article 5	WO pamphlet 02076995
Patent Article 6	Japanese Patent Laid-Open Publication No. Hei 2003-137894
Patent Article 7	WO Pamphlet 03040097
Patent Article 8	WO Pamphlet 02064616
Patent Article 9	WO Pamphlet 02062389
Patent Article 10	WO Pamphlet 03051876
Patent Article 11	WO Pamphlet 03061567
Patent Article 12	WO Pamphlet 03062248
Patent Article 13	WO Pamphlet 03062252
Patent Article 14	WO Pamphlet 03073986
Non-Patent Article 1	Y. Takuma et al., Mol. Cell. Endocrinol., 177, 3(2001)
Non-Patent Article 2	Y. Igarashi, Ann, N.Y. Acad. Sci., 845, 19(1998)
Non-Patent Article 3	H. Okazaki et al., Biochem. Biophs. Res. Commun., 190, 1104(1993)
Non-Patent Article 4	S. Mandala et al., Science, 296,346(2002)
Non-Patent Article 5	V. Brinkmann et al., J. Biol. Chem., 277, 21453(2002)

[0003] Sphingosine-1-phosphate (referred to simply as S1P, hereinafter), which was previously considered a more intermediate product in the metabolism of sphingosine, has proven to have an ability to facilitate cell growth and regulate cell motility. Studies have now shown that S1P, a previously unknown lipid mediator, is involved in a wide range of physiological actions, including apoptisis, modification of cell morphology and vascular contraction (Non-Patent Article 1 and Non-Patent Article 2). The lipid acts both as an intracellular second messenger and as an intercellular mediator; its role as an intercellular mediator has been particularly intensively studied. S1P induces signal transduction via a family of cell membrane G-protein-coupled receptors designated as Edg (which stands for Endothelial Differential Gene) (Non-Patent Article 1 and Non-Patent Article 3). Currently known subtypes of S1P receptors are Edg-1, Edg-3, Edg-5, Edg-6 and Edg-8, which are also referred to as $S1P_1$, SIP_3, SIP_2, SIP_4 and SIP_5, respectively.

[0004] Many studies of these S1P receptors suggest that S1P receptor modulators, which bind to these receptors and act as agonists or antagonists of S1P receptors, are effective against a broad spectrum of diseases. For example, compounds that act on Edg-5 have been shown effective against arteriosclerosis, renal fibrosis, pulmonary fibrosis and hepatic fibrosis (Patent Article 1). Compounds that act on Edg-1, Edg-3 or Edg-5 have been shown to be effective therapeutic or prophylactic agents against various respiratory diseases, including chronic bronchial asthma, diffuse pulmonary hamartoangiomyomatosis, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), interstitial pneumonia, idiopathic interstitial pneumonia, lung cancer and hypersensitivity pneumonitis (Patent Article 2). In addition, compounds that act as Edg-1 agonists have been shown to be effective therapeutic or prophylactic agents for peripheral vascular diseases, such as arteriosclerosis obliterans, thromboangiitis obliterans, Buerger's disease and diabetic neuropathy, septicemia, angiitis, nephritis, pneumonia, cerebral infarction, myocardial infarction, edema, arteriosclerosis, varicose veins, such as piles, anal fissure and anal fistula, dissecting arterial aneurysm, stenocardia, DIC, pleuritis, congestive heart failure, multiple organ failure, bed sore, burn, ulcerative colitis, Crohn's disease, heart transplantation, kidney transplantation, skin transplantation, liver transplantation, bone marrow transplantation, osteoporosis, chronic hepatitis, hepatic cirrhosis, chronic renal failure and glomerulosclerosis (Patent Article 3). Furthermore, compounds that act as agonists of S1P receptors have been shown to modulate the migration

of leukocytes (Non-Patent Article 4 and Non-Patent Article 5). Moreover, the derivatives mentioned in the aforementioned Non-Patent Articles have been shown effective not only against various organ transplants and GVHD, but also against autoimmune diseases, such as rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus, Hashimoto's disease, multiple sclerosis, myasthenia gravis, type I and type II diabetes and Crohn's disease, allergic diseases, such as atopic dermatitis, allergic rhinitis, allergic conjunctivitis, allergic contact dermatitis, and inflammatory diseases, such as inflammatory bowel disease and ulcerative colitis (Patent Article 4 and Patent Article 5). Phosphoric acid derivatives similar to what are described in Patent Articles 4 and 5 and act as antagonists of S1P receptors are described in Patent Article 6. Other S1P receptor modulators are disclosed in Patent Articles 7, 8, 9 and 10.

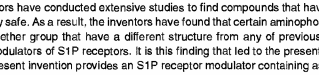
[0005] In the course of the studies to develop compounds that have an ability to modulate S1P receptors, which are involved in the onset of various disorders, the present inventors have drawn the attention to aminophosphonic acid derivatives having different structures from previously known compounds and have made an effort in searching for novel modulators of S1P receptors. Quite recently, S1P receptor agonists having an amino group along with a phosphonic acid unit were disclosed in Patent Articles 11, 12 and 13. Each of these compounds has a structure in which the amino group is integrated in their linking backbone. This structure differs from the structure of the compounds of the present invention, which essentially has the form of β-aminophosphonic acid or γ-aminophosphonic acid in which an amino group exists on the linking backbone. Patent Article 14 describes similar compounds but the compounds of the present invention are not included.

DISCLOSURE OF THE INVENTION

[0006] It is thus an objective of the present invention to provide an aminophophonic acid derivative that can effectively modulate S1P receptors with less side effects.

[0007] The present inventors have conducted extensive studies to find compounds that have an ability to modulate S1P receptors and are highly safe. As a result, the inventors have found that certain aminophosphonic acid derivatives with a diarylsulfide or diarylether group that have a different structure from any of previously known S1P receptor modulators act as potent modulators of S1P receptors. It is this finding that led to the present invention.

[0008] Accordingly, the present invention provides an S1P receptor modulator containing as an active ingredient at least one of aminophosphonic acid derivatives represented by the following general formula (1):

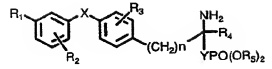


(1)

[wherein R_1 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a hydroxy group, a pheny group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a substituted or unsubstituted phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms. an aralkyl group or an aralkyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; R_4 is a hydrogen atom, a halogen atom, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxymethyl group having 1 to 4 carbon atoms, a lower alkylthiomethyl group having 1 to 4 carbon atoms, a hydroxymethyl group, a phenyl group or an aralkyl group; R_5 is a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms: X is O, S, SO or SO_2; Y is $-CH_2O-$, $-CH_2-$, $-CH=CH-$, $-CH=CF-$, $-CH_2CH_2-$, $-CH_2CFH-$, $-CH_2CF_2-$or $-CH(OH)CF_2-$; and n is an integer from 1 to 4], and an optical isomer, and a pharmaceutically acceptable salt and a hydrate thereof.

[0009] More specifically,

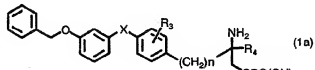
(I) the present invention provides: an aminophosphonic acid derivative represented by the following general formula (1) :



(1)

[wherein R_1, R_2, R_3, R_4, R_5, Y and n are as defined above], and an optical isomer, and a pharmaceutically acceptable salt and a hydrate thereof;

(II) 2-aminophosphonic acid monoester derivative represented by the following general formula (1a):

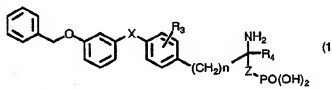


(1a)

[wherein R_3, R_4, X and n are as defined above], and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof;

(III) 2-aminophosphonic acid monoester derivative represented by the general formula (1a) and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof;

(IV) 3-aminophosphonic acid derivative represented by the following general formula (1b):



(1b)

[wherein z is CH_2-, -CH=CH-, -CH=CF-, $-CH_2CH_2$-, $-CH_2CHF$-, $-CH_2CF_2$- or $-CH(OH)CF_2$-; and R_3, R_4, X and n are as defined above], and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof;

(V) 3-aminophosphonic acid derivative represented by the general formula (1b), and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof, wherein R_3 is a chlorine atom; and

(VI) An S1P receptor modulator containing as an active ingredient at least one of the compounds of (I) to (V) above.

[0010] The compounds of the general formulae (1), (1a) and (1b) are novel compounds.

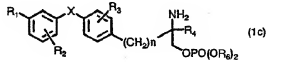
[0011] Among preferred compounds of the present invention are aminophosphonic acid ester derivatives according to claim 1, including 1) 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentylphosphonic acid monoester, 2) 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutylphosphonic acid monoester, 3) 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylpentylphosphonic acid monoester, 4) 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonic acid monoester, 5) 3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylpentylphosphonic acid and 6) 3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylhexylphosphonic acid, and pharmaceutically acceptable salts and hydrates thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0012] Pharmaceutically acceptable alkaline salts of the compounds represented by the general formula (1) according to the present invention include sodium salts, potassium salts, magnesium salts, calcium salts and aluminum salts. Acid salts of the compounds represented by the general formula (1) include hydrochlorides, hydrobromides, acetates, trifluoroacetates, methanesulfonates, citrates and tartarates.

[0013] The halogen atom in the general formula (1) may be fluorine, chlorine, bromine or iodine. The lower alkyl group as in the "lower alkyl group having 1 to 4 carbon atoms", the "lower alkoxy group having 1 to 4 carbon atoms", the "lower alkylthio group having 1 to 4 carbon atoms" , the "lower alkyl group sulfinyl having 1 to 4 carbon atoms", the "lower alkyl sulfonyl group having 1 tc 4 carbon atoms" or the "lower alkoxymethyl group having 1 to 4 carbon atoms" in the general formula (1) is a straight-chained or branched hydrocarbon having 1 to 4 carbon atoms, including methyl, ethyl, propyl, isopropyl, butyl and t-butyl. The "substituted or unsubstituted phenoxy group" or "substituted or unsubstituted aralkyl group" in the general formula (1) is a phenoxy or aralkyl group that has at some position on its benzene ring a halogen atom, such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, a trifluromethyl group, a lower alkyl group having 1 to 4 carbon atoms or a lower alkoxy group having 1 to 4 carbon atoms. The "aralkyl group" as in "aralkyl group" or "aralkyloxy group" in the general formula (1) may be a benzyl group, a diphenylmethyl group, a phenethyl group or a phenylprooyl group.

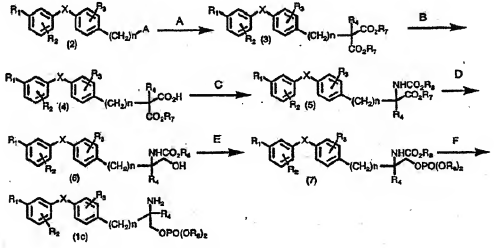
[0014] Of the compounds represented by the general formula (1) according to the present invention, those in which Y is $-CH_2O-$ and R_5 is a lower alkyl group having 1 to 4 carbon atoms, which are represented by the following general formula (1c):



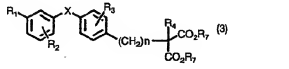
(1c)

(wherein R_6 is a lower alkyl group having 1 to 4 carbon atoms; and R_1, R_2, R_3, R_4, X and n are as defined above) can be produced through the following pathway:

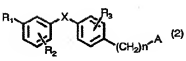
Synthetic pathway 1



[0015] In the synthetic pathway 1, the compound represented by the following general formula (3):

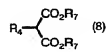


(wherein R_7 is a lower alkyl group having 1 to 4 carbon atoms; and R_1, R_2, R_3, R_4, X and n are as defined above) can be obtained by reacting a compound represented by the following general formula (2):



(2)

(wherein A is a chlorine atom, a bromine atom or an iodine atom, and R_1, R_2, R_3, X and n are as defined above) with a compound represented by the following general formula (8):

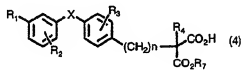


(8)

(wherein R_4 and R_7 are as defined above) in the presence of a base (Step A).

[0016] This reaction may use methanol, ethanol, 1,4-dioxane, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF) or tetrahydrofurane (THF) as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate and sodium carbonate.

[0017] In the synthetic pathway 1, the compound represented by the following general formula (4):

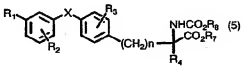


(4)

(wherein R_1, R_2, R_3, R_4, R_7, X and n are as defined above) can be obtained by hydrolysis of the compound of the general formula (3) (Step B).

[0018] This reaction may use methanol, ethanol, 1,4-dioxane, DMF or DMSO as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature and in the presence of a base, such as aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide. Preferably, the compound of the general formula (3) is reacted with potassium hydroxide in an ethanol solvent at 50°C.

[0019] In the synthetic pathway 1, the compound represented by the following general formula (5):

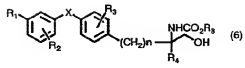


(5)

(wherein R_8 is a lower alkyl group having 1 to 4 carbon atoms; and R_1, R_2, R_3, R_4, R_7, X and n are as defined above) can be obtained by allowing the compound of the general formula (4) to undergo Curtis rearrangement (Step C).

[0020] This reaction can be carried out by using common techniques for converting a carboxyl group into a carbamate. One such technique involves the use of ethyl chlorocarbonate and NaN_3. Another preferred technique involves heating diphenylphosphoryl azide (DPPA) in a benzene or toluene solvent in the presence of a base such as triethylamine while stirring the mixture, followed by addition of a lower alcohol such as methanol, ethanol, propanol, isopropanol, butanol and t-butanol and then further heating while stirring the mixture. Alternatively, the reaction may use only a lower alcohol as a reaction solvent and is carried out by heating and stirring the mixture and, preferably, by heat-refluxing the mixture.

[0021] In the synthetic pathway 1, the compound represented by the following general formula (5):

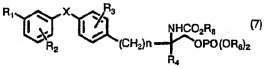


(6)

(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be obtained by the reduction of the compound of the general formula (5) (Step D).

[0022] This reaction may use an alkylborane derivative such as borane (BH_3) and 9-borabicyclo[3.3.1]nonane (9-BBN) and a metal hydride complex such as diisobutylaluminum hydride ($(iBu)_2AlH$), sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), preferably lithium borohydride ($LiBH_4$), and uses THF, 1,4-dioxane, ethanol or methanol as a reaction solvent. The reaction may typically be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature.

[0023] In the synthetic pathway 1, the compound represented by the following general formula (7):



(7)

(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (6) with a compound represented by the following general formula (9):

$$P(OR_8)_3 \qquad (9)$$

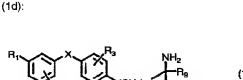
(wherein R_8 is as described above) (Step E).

[0024] This reaction may be carried out without any solvent or by using methylene chloride, chloroform, acetonitrile, ethyl acetate, THF or ether as a dilution solvent and may be carried out at a reaction temperature of 0°C to room temperature and in the presence of carbon tetrabromide and pyridine.

[0025] In the synthetic pathway 1, the compound of the general formula (1c) can be obtained by acidolysis or hydrolysis of the compound of the general formula (7) (Step F).

[0026] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

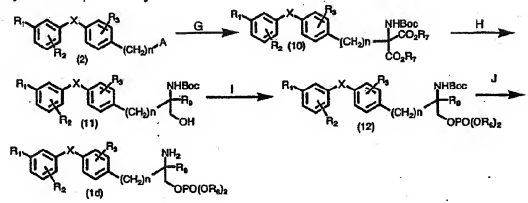
[0027] Of the compounds represented by the general formula (1), those in which R_4 is a hydrogen atom or a hydroxymethyl group, R_5 is a lower alkyl group having 1 to 4 carbon atoms and Y is - CH_2O and which are represented by the following general formula (1d):



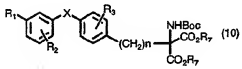
(1d)

(wherein R_9 is a hydrogen atom or a hydroxymethyl group; and R_1, R_2, R_3, R_6, X and n are as defined above) can be produced through the following pathway:

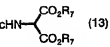
Synthetic pathway 2



[0028] In the synthetic pathway 2, the compound represented by the following general formula (10):



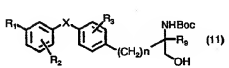
(wherein Boc is t-butoxycarbonyl group; and R_1, R_2, R_3, R_7, X and n are as defined above) can be obtained by reacting the compound of the general formula (2) with a compound represented by the following general formula (13):



(wherein R_7 and Boc are as defined above) in the presence of a base (Step G).

[0029] This reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, potassium alkoxide, potassium carbonate and sodium carbonate.

[0030] In the synthetic pathway 2, the compound represented by the following general formula (11):

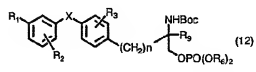


(wherein R_1, R_2, R_3, R_9, X, Boc and n are as defined above) can be obtained by reduction of the compound of the general formula (10) (Step H).

[0031] This reaction may use an alkylborane derivative such as BH_3 and 9-BBN and a metal hydride complex such as $(iBu)_2AlH$, $NaBH_4$ and $LiAlH_4$, preferably $LiBH_4$, and uses THF, 1,4-dioxane, ethanol or methanol as a reaction solvent. The reaction may be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room

temperature.

[0032] In the synthetic pathway 2, the compound represented by the following general formula (12):



(12)

(wherein R_1, R_2, R_3, R_6, R_9, X, Boc and n are as defined above) can be obtained by reacting the compound of the general formula (11) with a compound represented by the following general formula (9) :

$$P(OR_6)_3 \quad (9)$$

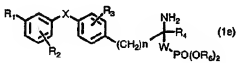
(wherein R_6 is as described above) (Step I).

[0033] This reaction may be carried out without any solvent or by using methylene chloride, chloroform, acetonitrile, ethyl acetate, THF or ether as a solvent and may be carried out at a reaction temperature of 0°C to room temperature and in the presence of carbon tetrabromide and pyridine.

[0034] In the synthetic pathway 2, the compound of the general formula (1d) can be obtained by acidolysis of the compound of the general formula (12) (Step J).

[0035] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature.

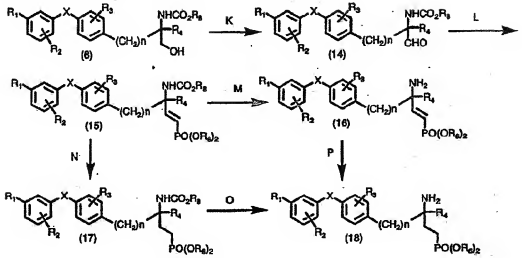
[0036] Of the compounds represented by the general formula (1), those in which Y is -CH=CH- or $-CH_2-CH_2-$ and R_5 is a lower alkyl group, which are represented by the following general formula (1e):



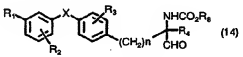
(1e)

(wherein W is -CH=CH- or $-CH_2-CH_2-$; and R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be produced through the following synthetic pathway 3:

Synthetic pathway 3



[0037] In the synthetic pathway 3, the compound represented by the following general formula (14):

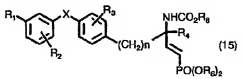


(14)

(wherein R_1, R_2, R_3, R_4, R_8, X and n are as defined above) can be obtained by oxidation of the compound of the general formula (6) (Step K).

[0038] This reaction may be carried out using a common technique for oxidizing alcohol into aldehyde. Among agents used in these techniques are chromium oxide/pyridine complexes, such as pyridinium chlorochromate and pyridinium dichromate, and metal oxidizing agents, such as chromium oxide, silver carbonate and manganese dioxide. DMSO oxidation using DMSO activating agents, such as oxalyl chloride, anhydrous trifluoroacetic acid, anhydrous acetic acid, DCC and sulfur trioxide/pyridine complex, may also be employed.

[0039] In the synthetic pathway 3, the compound represented by the following general formula (15):



(15)

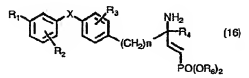
(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (14) with a compound represented by the following general formula (19):

(19)

(wherein R_6 are as defined above) in the presence of a base (Step L).

[0040] This reaction may use THF, ether or 1,4-dioxane as a reaction solvent and can be carried out at a reaction temperature of -78°C to room temperature and in the presence of sodium hydride, potassium hydride, sodium alkoxide or potassium alkoxide, preferably n-butyllithium.

[0041] In the synthetic pathway 3, the compound represented by the following general formula (16):

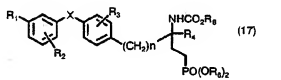


(16)

(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be obtained by acidolysis or hydrolysis of the compound of the general formula (15) (Step M).

[0042] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and is preferably carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

[0043] In the synthetic pathway 3, the compound represented by the following general formula (17):

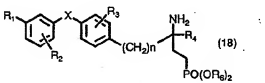


(17)

(wherein R_1, R_2, R_3, R_4, R_6, R_9, X and n are as defined above) can be obtained by reduction of the compound of the general formula (15) (Step N).

[0044] This reaction can be carried out in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon and ruthenium carbon, and in such a solvent as ethanol, methanol, THF, DMF and ethyl acetate and is carried out at room temperature under a hydrogen pressure of atmospheric or higher pressure.

[0045] In the synthetic pathway 3, the compound represented by the following general formula (18):



(18)

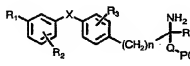
(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be obtained by acidolysis or hydrolysis of the compound of the general formula (17) (Step O).

[0046] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

[0047] The compound of the general formula (18) can also be obtained by reduction of the compound of the general formula (16) (Step P). In such a case, the reaction may be carried out in the presence of a reduction catalyst, such as

palladium carbon, platinum carbon, platinum oxide, rhodium carbon and ruthenium carbon, and in such a solvent as ethanol, methanol, THF, DMF and ethyl acetate and may be carried out under a hydrogen pressure of atmospheric or higher pressure at room temperature.

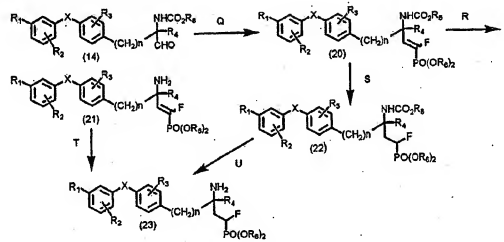
[0048] Of the compounds represented by the general formula (1), those in which Y is -CH=CF- or -CH_2CHF- and R_5 is a lower alkyl group having 1 to 4 carbon atoms, which are represented by the following general formula (If):



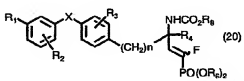
(If)

(wherein Q is -CH=CF- or -CH_2CHF-; and R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be produced through the following synthetic pathway 4:

Synthetic pathway 4



[0049] In the synthetic pathway 4, the compound represented by the following general formula (20):



(20)

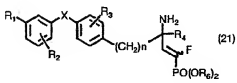
(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (14) with the compound represented by the following general formula (24):

$$FBr_2CPO(OR_6)_2 \qquad (24)$$

(wherein R_6 is as defined above) in the presence of chlorotrimethylsilane (Step Q).

[0050] This reaction may use n-butyllithium or lithium diisopropylamide as a base and 1,4-dioxane, ether or, preferably, THF as a solvent and may be carried out at -78°C to 0°C.

[0051] In the synthetic pathway 4, the compound represented by the following general formula (21):

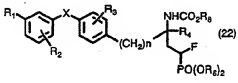


(21)

(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be obtained by acidolysis or hydrolysis of the compound of the general formula (20) (Step R).

[0052] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C; and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

[0053] In the synthetic pathway 4, the compound represented by the following general formula (22):

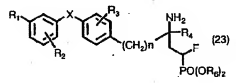


(22)

(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reduction of the compound of the general formula (20) (Step S).

[0054] This reaction can be carried out in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon and ruthenium carbon, and in such a solvent as ethanol, methanol, THF, DMF and ethyl acetate and may be carried out at room temperature under a hydrogen pressure of atmospheric or higher pressure.

[0055] In the synthetic pathway 4, the compound represented by the following general formula (23):



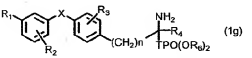
(23)

(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be obtained by reduction of the compound of the general formula (21) (Step T) or acidolysis or hydrolysis of the compound of the general formula (22) (Step U).

[0056] This reduction process can be carried out in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon and ruthenium carbon, and in such a solvent as ethanol, methanol, THF, DMF and ethyl acetate and may be carried out at room temperature under a hydrogen pressure of atmospheric or higher pressure. The acidolysis or hydrolysis process may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature,

preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

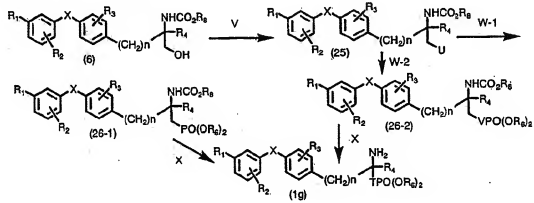
[0057] Of the compounds represented by the general formula (1), those in which R_5 is a lower alkyl group having 1 to 4 carbon atoms and Y is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CHF-$ or $-CH_2CF_2-$, which are represented by the following general formula (1g):



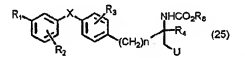
(1g)

(wherein T is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CHF-$ or $-CH_2CF_2-$; and R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be produced through the following synthetic pathway 5:

Synthetic pathway 5



[0058] In the synthetic pathway 5, the compound represented by the following general formula (25):



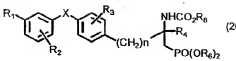
(25)

(wherein U is an iodine atom, a bromine atom, a methanesulfonyloxy group or a trifluoromethanesulfonyloxy group; and R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be produced from the compound of the general formula (6) (Step V).

[0059] For the introduction of methanesulfonyloxy group or trifluoromethanesulfonyloxy group, an organic solvent such as methylene chloride, chloroform, ethyl acetate and THF is used along with a base such as triethylamine, diisopropylethylamine, pyridine, lutidine and 2,4,6-trimethylpyridine, and the compound of the general formula (6) is preferably reacted with methanesulfonyl chloride or anhydrous trifluoromethanesulfonate at -45°C to room temperature.

[0060] The brominated or iodized compound is synthesized by reacting the methanesulfonyloxylated product obtained in the above process with sodium bromide, sodium iodide, potassium bromide, potassium iodide, lithium bromide or lithium iodide at room temperature to reflux temperature in a solvent such as toluene, benzene or THF.

[0061] In the synthetic pathway 5, the compound represented by the following general formula (26-1):


(26-1)

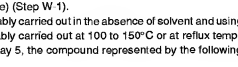
(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (25) with a compound represented by the following general formula (27):

$$PO(OR_6)_3 \quad (27)$$

(wherein R_6 is as defined above) (Step W-1).

[0062] This reaction is preferably carried out in the absence of solvent and using the compound of the general formula (27) as a solvent and is preferably carried out at 100 to 150°C or at reflux temperature.

[0063] In the synthetic pathway 5, the compound represented by the following general formula (26-2):


(26-2)

(wherein V is a fluorinated or unfluorinated methylene group; and R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (25) with a compound represented by the following general formula (28) :

$$HVPO(OR_6)_2 \quad (28)$$

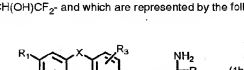
(wherein R_6 and V are as defined above) in the presence of a base (Step W-2).

[0064] This reaction may be carried out in the presence of such a base as lithium diisopropylamide, lithium hexamethyldisilazide and lithium tetramethylpiperidide in such a reaction solvent as THF and 1,4-dioxane and may be carried out at a reaction temperature of -78°C to room temperature.

[0065] In the synthetic pathway 5, the compound of the general formula (1g) can be obtained by acidolysis or hydrolysis of the compound of the general formula (26-1) or (26-2) (Step X).

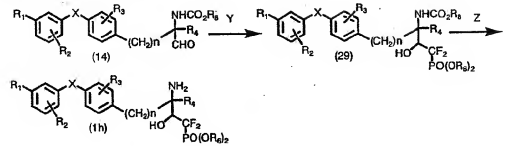
[0066] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

[0067] Of the compounds represented by the general formula (1), those in which R_8 is a lower alkyl group having 1 to 4 carbon atoms and Y is $-CH(OH)CF_2-$ and which are represented by the following general formula (1h):

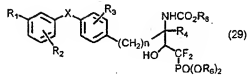

(1h)

(wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined above) can be synthesized through the following synthetic pathway 6:

Synthetic pathway 6



[0068] In the synthetic pathway 6, the compound represented by the following general formula (29):



(29)

(wherein R_1, R_2, R_3, R_4, R_6, R_8, X and n are as defined above) can be obtained by reacting the compound of the general formula (14) with a compound represented by the following general formula (30):

$$HCF_2PO(OR_6)_2 \quad (30)$$

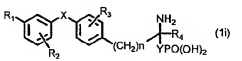
(wherein R_6 is as defined above) in the presence of a base (Step Y).

[0069] This reaction may use n-butyllithium, preferably lithium diisopropylamide, as a base and 1,4-dioxane or ether, preferably THF, as a solvent and may be carried out at -78°C to 0°C.

[0070] In the synthetic pathway 6, the compound of the general formula (1h) can be obtained by acidolysis or hydrolysis of the compound of the general formula (29) (Step Z).

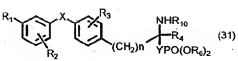
[0071] This reaction may be carried out in an inorganic acid or organic acid such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid or in a mixture with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane and ethyl acetate and may be carried out at a reaction temperature of 0°C to room temperature. Alternatively, the reaction may use methanol, ethanol, 1,4-dioxane, DMSO, DMF or THF as a reaction solvent and may be carried out at a reaction temperature of 0°C to reflux temperature, preferably 80°C to 100°C, and in the presence of a base such as an aqueous solution of sodium hydroxide, potassium hydroxide or lithium hydroxide.

[0072] Of the compounds represented by the general formula (1), those in which R_5 is hydrogen and which are represented by the following general formula (1i):



(1i)

(wherein R_1, R_2, R_3, R_4, X, Y and n are as defined above) can be obtained by acidolysis or treatment with trimethylsilyl bromide or trimethylsilyl iodide of the compound represented by the following general formula (31):



(31)

(wherein R_{10} is a hydrogen atom or a lower alkoxycarbonyl group having 1 to 4 carbon atoms ; and R_1, R_2, R_3, R_4, R_5, X, Y and n are as defined above).

[0073] The acidolysis process is preferably carried out in an inorganic acid such as hydrochloric acid and hydrobromic acid or in a mixture with an organic acid such as methanol and ethanol and is preferably carried out at reflux temperature.

[0074] Alternatively, the reaction may use acetonitrile or methylene chloride as a solvent and the compound of the general formula (31) may be treated with trimethylsilyl bromide or trimethylsilyl iodide, or the combination of trimethylsilyl chloride and sodium bromide or sodium iodide. In such a case; the reaction is preferably carried out at 0°C to room temperature.

[0075] The compounds of the respective general formulae in which X is SO or SO_2 may also be obtained by oxidation of the corresponding compounds in which X is S.

[0076] Such a reaction may use 1,4-dioxane, DMSO, DMF, THF, methylene chloride or chloroform as a reaction solvent and potassium permanganate, m-chlorobenzoic acid or aqueous hydrogen peroxide as an oxidizing agent and is preferably carried out at 0°C to reflux temperature, preferably at room temperature.

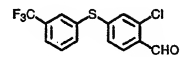
Examples

[0077] The present invention will now be described with reference to specific examples, which are not intended to limit the scope of the invention in any way.

<Reference Example 1>

2-chloro-4-[(3-trifluoromethyl)phenylthio]benzaldehyde

[0078]

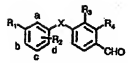


[0079] To a DMF solution (20mL) of 2-chloro-4-fluorobenzaldehyde(1.15g) and 3-(trifluoromethyl)thiophenol(1.33g), potassium carbonate (2.78g) was added and the mixture was stirred for 1 hour at 120°C. Subsequently, the reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 10 : 1). This gave the desired product as a pale yellow oil (1.96g).

<Reference Examples 2 through 57>

[0080] In a similar manner to Reference Example 1, different thiophenols and phenols were used to synthesize the different compounds shown in Table 1 below.

Table 1

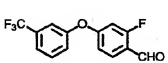


Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
2	Cl	o-Cl	H	Cl	O	30	i-PrO	o-iPr	H	Cl	O
3	t-Bu	H	H	H	O	31	i-PrO	o-iPr	H	H	O
4	Me	H	H	H	O	32	PhO	H	H	Cl	O
5	i-Pr	o-i-Pr	H	Cl	O	33	$PhCH_2O$	H	H	H	O
6	C_5H_{11}	H	H	H	O	34	$PhCH_2O$	H	H	Br	O
7	C_7H_{15}	H	H	H	O	35	$PhCH_2O$	H	H	SMe	O
8	CF_3	H	H	H	O	36	$PhCH_2O$	H	H	Me	O
9	CF_3	H	OMe	H	O	37	$PhCH_2O$	H	H	Et	O
10	CF_3	H	H	OMe	O	38	$PhCH_2O$	o-Cl	H	Cl	O
11	CF_3	H	H	OCH_2Ph	O	39	$PhCH_2O$	H	H	CF_3	O
12	CF_3	H	CF_3	H	O	40	$PhCH_2O$	H	H	Ph	O
13	CF_3	H	H	CF_3	O	41	$PhCH_2O$	o-$PhCH_2O$	H	Cl	O
14	CF_3	o-CF_3	H	H	O	42	$PhCH_2O$	o-$PhCH_2O$	H	H	O
15	CF_3	o-CF_3	H	Cl	O	43	$PhCH_2O$	o-$PhCH_2O$	H	i-Pr	O
16	CF_3	b-Cl	H	H	O	44	MeO	o-CF_3	H	H	O
17	CF_3	a-Cl	H	H	O	45	MeS	H	H	H	O
18	CF_3	d-Cl	H	H	O	46	$PhCH_2S$	H	H	H	O
19	CF_3	c-MeO	H	Cl	O	47	$PhCH_2S$	H	H	Cl	O
20	$Ph(CH_2)_2$	H	H	Cl	O	48	Cl	o-Cl	H	H	S
21	$Ph(CH_2)_2$	H	H	CF_3	O	49	CF_3	o-CF_3	H	Cl	S
22	$Ph(CH_2)_2$	o-CF_3	H	H	O	50	CF_3	o-CF_3	H	H	S
23	$Ph(CH_2)_2$	o-CF_3	H	Cl	O	51	CF_3	H	H	H	S
24	$Ph(CH_2)_2$o-$Ph(CH_2)_2$	H	H	O	52	CF_3	H	H	CF_3	S
25	$Ph(CH_2)_2$o-$Ph(CH_2)_2$	H	CF_3	O	53	MeO	H	H	Cl	S
26	$Ph(CH_2)_2$o-$Ph(CH_2)_2$	H	Cl	O	54	MeO	H	H	H	S
27	CF_3	o-NO_2	H	H	O	55	MeO	H	H	CF_3	S
28	CF_3	H	Cl	H	O	56	$PhCH_2O$	H	H	Cl	O
29	CF_3	H	H	Cl	O	57	$PhCH_2O$	H	H	i-Pr	O

<Reference Example 58>

2-fluoro-4-[(3-trifluoromethyl)phenoxy]benzaldehyde

[0081]



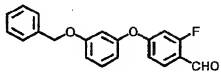
[0082] 3-(trifluoromethyl)phenylboric acid (1.03g) and 2-fluoro-4-hydroxybenzaldehyde (760mg) were dissolved in

methylene chloride (20mL). While the mixture was stirred, copper acetate (985mg), molecular sieve 4A (800mg) and triethylamine (3.76mL) were added to the mixture. An equal amount of copper acetate was added after 8 hours and after 24 hours. After 48 hours of stirring, the insoluble materials were removed by filtration and the filtrate was poured in water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 7 : 1 then 2 : 1). This gave the desired product as a pale yellow oil (265mg).

<Reference Example 59>

4-[(3-benzyloxy)phenoxy]-2-fluorobenzaldehyde

[0083]

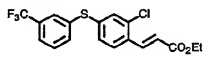


[0084] In a similar manner to Reference Example 58, 3-benzyloxyphenylboric acid and 2-fluoro-4-hydroxybenzaldehyde were used to obtain the desired product as a colorless oil.

<Reference Example 60>

Ethyl 2'-chloro-4'-[(3-trifluoromethyl)phenylthio]cinnamate

[0085]

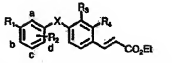


[0086] At 0°C and under a stream of argon gas, 60% sodium hydride (272mg) was added to a THF solution (30mL) of ethyl diethylphosphonoacetate (1.35mL). The mixture was stirred for 30min and a THF solution (15mL) of the compound of Reference Example 1 (1.96g) was added dropwise. The mixture was stirred for 2 hours while kept at the same temperature. This was followed by addition of water and extraction with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10: 1). This gave the desired product as a colorless oil (1.72g).

<Reference Examples 61 through 118>

[0087] In a similar manner to Reference Example 60, the compounds of Reference Examples 2 through 59 were used to synthesize the compounds shown in Table 2 below.

Table 2

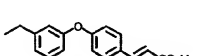


Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
61	Cl	o-Cl	H	Cl	O	90	i-PrO	o-iPr	H	Cl	O
62	t-Bu	H	H	H	O	91	i-PrO	o-iPr	H	H	O
63	Me	H	H	H	O	92	PhO	H	H	Cl	O
64	i-Pr	o-i-Pr	H	Cl	O	93	$PhCH_2O$	H	H	H	O
65	C_5H_{11}	H	H	H	O	94	$PhCH_2O$	H	H	Br	O
66	C_7H_{15}	H	H	H	O	95	$PhCH_2O$	H	H	SMe	O
67	CF_3	H	H	H	O	96	$PhCH_2O$	H	H	Me	O
68	CF_3	H	OMe	H	O	97	$PhCH_2O$	H	H	Et	O
69	CF_3	H	H	OMe	O	98	$PhCH_2O$	o-Cl	H	Cl	O
70	CF_3	H	H	OCH_2Ph	O	99	$PhCH_2O$	H	H	CF_3	O
71	CF_3	H	CF_3	H	O	100	$PhCH_2O$	H	H	Ph	O
72	CF_3	H	H	CF_3	O	101	$PhCH_2O$	o-$PhCH_2O$	H	Cl	O
73	CF_3	o-CF_3	H	H	O	102	$PhCH_2O$	o-$PhCH_2O$	H	H	O
74	CF_3	o-CF_3	H	Cl	O	103	$PhCH_2O$	o-$PhCH_2O$	H	i-Pr	O
75	CF_3	b-Cl	H	H	O	104	MeO	o-CF_3	H	H	O
76	CF3	a-Cl	H	H	O	105	MeS	H	H	H	O
77	CF3	d-Cl	H	H	O	106	$PhCH_2S$	H	H	H	O
78	CF_3	o-MeO	H	Cl	O	107	$PhCH_2S$	H	H	Cl	O
79	$Ph(CH_2)_2$	H	H	Cl	O	108	Cl	o-Cl	H	H	S
80	$Ph(CH_2)_2$	H	H	CF_3	O	109	CF_3	o-CF_3	H	Cl	S
81	$Ph(CH_2)_2$	o-CF_3	H	H	O	110	CF_3	o-CF_3	H	H	S
82	$Ph(CH_2)_2$	o-CF_3	H	Cl	O	111	CF_3	H	H	H	S
83	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	H	O	112	CF_3	H	H	CF_3	S
84	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	CF_3	O	113	MeO	H	H	Cl	S
85	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	Cl	O	114	MeO	H	H	H	S
86	CF_3	H	H	F	O	115	MeO	H	H	CF_3	S
87	$PhCH_2O$	H	H	F	O	116	CF_3	o-NO_2	H	H	O
88	CF_3	H	Cl	H	O	117	$PhCH_2O$	H	H	Cl	O
89	CF_3	H	H	Cl	O	118	$PhCH_2O$	H	H	i-Pr	O

<Reference Example 119>

Methyl 4'-(3-ethylphenoxy)cinnamate

[0088]

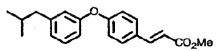


[0089] To a DMF solution (50mL) of 3-ethylphenol (1.13g) and methyl 4'-fluorocinnamate (834mg), potassium carbonate (1 92g) was added and the mixture was stirred for 8 hours at 140°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 30: 1). This gave the desired product as a yellow oil (540mg).

<Reference Example 120>

Methyl 4'-(3-isobutylphenoxy)cinnamate

[0090]

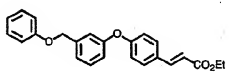


[0091] To a DMF solution (10mL) of 3-isobutylphenol (451mg) and methyl 4'-fluorocinnamate (541mg), potassium carbonate (622mg) was added and the mixture was stirred for 8 hours at 140°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 30: 1). This gave the desired product as a yellow oil (278mg).

<Reference Example 121>

Ethyl 4'-[(3-phenoxymethyl)phenoxy]cinnamate

[0092]

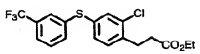


[0093] The compound of Reference Example 63 (2.82g) was dissolved in tetrachlorocarbon (50mL). To this solution, N-bromosuccinimide (2.31g) was added and the mixture was stirred while heated and exposed to light. After 24 hours, the solvent was removed under reduced pressure and the resulting residue was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 6 : 1). This gave ethyl 4'-[(3-bromomethyl) phenoxy]cinnamate as a yellow oil (1.30g). The resultant brominated product (1.24g) was dissolved in DMF (25mL). To this solution, phenol (380mg) and potassium carbonate (500mg) were added and the mixture was stirred for 3 hours at 60°C. The reaction mixture was poured into water and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4 : 1). This gave the desired product as a colorless oil (1.30g).

<Reference Example 122>

Ethyl 2'-chloro-4'-(3-trifluoromethylphenylthio)dihydrocinnamate

[0094]

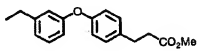


[0095] The compound of Reference Example 60 (1.72g) was dissolved in ethanol (70mL). While the solution was stirred at 0°C, bismuth chloride (703mg) was added. Subsequently, sodium borohydride (673mg) was added in small portions and the mixture was stirred for 1 hour at this temperature and 3 hours at room temperature. Ice water was added and the crystallized insoluble inorganic residue was removed by filtration through Celite. The filtrate was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (1.50g) (Process A).

<Reference Example 123>

Methyl 4'-(3-ethylphenoxy)dihydrocinnamate

[0096]

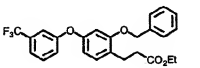


[0097] The compound of Reference Example 119 (540mg) was dissolved in ethanol (20mL) and 10%-Pd/C (80.0mg) was added. Under a stream of hydrogen, the mixture was stirred at room temperature for 3 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give the desired product as a colorless oil (Process B).

<Reference Example 124>

Ethyl 2'-benzyloxy-4'-[(3-trifluoromethyl)phenoxy]dihydrocinnamate

[0098]

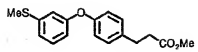


[0099] The compound of Reference Example 70 (2.29mg) was dissolved in ethyl acetate (30mL) and 5%-Pd/C-ethylenediamine complex (230mg) was added. Under a stream of hydrogen, the mixture was stirred at room temperature for 3.5 hours. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give the desired product as a pale yellow oil (2.30g) (Process C).

<Reference Example 125>

Methyl 4'-[(3-methylthio)phenoxy]dihydrocinnamate

[0100]



[0101] Under a stream of argon gas, the compound of Reference Example 105 (4.07g) was dissolved in methanol (50mL). While the solution was stirred at 10°C, magnesium (1.00g) was added. The mixture was stirred for 3 hours while kept at this temperature, and diluted hydrochloric acid was added. The mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (3.70g) (Process D).

<Reference Examples 126 through 182>

[0102] Similarly, the compounds of Reference Examples 61 through 69, 71 through 104, 106 through 116, 117 and 118, and 120 and 121 were used to synthesize the compounds shown in Table 3 below.

Table 3

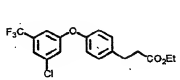
Reference Examples	R1	R2	R3	R4	X	Process	Reference Examples	R1	R2	R3	R4	X	Process
126	Cl	c-Cl	H	Cl	O	A	155	i-PrO	c-iPr	H	Cl	O	C
127	t-Bu	H	H	H	O	B	156	i-PrO	c-iPr	H	H	O	B
128	Me	H	H	H	O	B	157	PhO	H	H	Cl	O	A
129	i-Pr	c-i-Pr	H	Cl	O	A	158	$PhCH_2O$	H	H	H	O	A
130	C_6H_{11}	H	H	H	O	B	159	$PhCH_2O$	H	H	Br	O	A
131	C_7H_{15}	H	H	H	O	B	160	$PhCH_2O$	H	H	SMe	O	A
132	CF_3	H	H	H	O	B	161	$PhCH_2O$	H	H	Me	O	A
133	CF_3	H	OMe	H	O	B	162	$PhCH_2O$	H	H	Et	O	A
134	CF_3	H	H	OMe	O	B	163	$PhCH_2O$	c-Cl	H	Cl	O	A
135	CF_3	H	CF_3	H	O	B	164	$PhCH_2O$	H	H	CF_3	O	A
136	CF_3	H	H	CF_3	O	B	165	$PhCH_2O$	H	H	Ph	O	A
137	CF_3	c-CF_3	H	H	O	B	166	$PhCH_2O$	c-$PhCH_2O$	H	Cl	O	A
138	CF_3	c-CF_3	H	Cl	O	B	167	$PhCH_2O$	c-$PhCH_2O$	H	H	O	A
139	CF_3	b-Cl	H	H	O	A	168	$PhCH_2O$	c-$PhCH_2O$	H	i-Pr	O	A
140	CF3	a-Cl	H	H	O	A	169	MeO	c-CF_3	H	H	O	B
141	CF3	d-Cl	H	H	O	A	170	$PhCH_2S$	H	H	H	O	A
142	CF_3	c-MeO	H	Cl	O	B	171	$PhCH_2S$	H	H	Cl	O	A
143	$Ph(CH_2)_2$	H	H	Cl	O	A	172	Cl	H	H	H	S	D
144	$Ph(CH_2)_2$	H	H	CF_3	O	B	173	CF_3	c-CF_3	H	Cl	S	A
145	$Ph(CH_2)_2$	c-CF_3	H	H	O	B	174	CF_3	c-Me	H	H	S	D
146	$Ph(CH_2)_2$	c-CF_3	H	Cl	O	A	175	CF_3	H	H	H	S	A
147	$Ph(CH_2)_3$	c-$Ph(CH_2)_3$	H	H	O	B	176	CF_3	H	H	CF_3	S	A
148	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	CF_3	O	B	177	MeO	H	H	Cl	S	A
149	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	Cl	O	A	178	MeO	H	H	H	S	A
150	CF_3	H	H	F	O	B	179	MeO	H	H	CF_3	S	A
151	$PhCH_2O$	H	H	F	O	A	180	i-Bu	H	H	H	O	B
152	$PhOCH_2$	H	H	H	O	A	181	$PhCH_2O$	H	H	Cl	O	A
153	CF_3	H	Cl	H	O	A	182	$PhCH_2O$	H	H	iPr	O	A
154	CF_3	H	H	Cl	O	A							

D=Methyl ester

<Reference Example 183>

Ethyl 4'-[3-chloro-5-(trifluoromethyl)phenoxy]dihydrocinnamate

[0103]



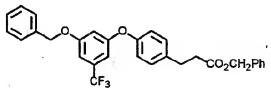
[0104] The compound of Reference Example 116 was reacted in the same manner as in Reference Example 124 to obtain ethyl 4'-[3-amino-5-(trifluoromethyl)phenoxy]dihydrocinnamate. An MeCN solution (15mL) containing this

compound (1.27g) was added to an MeCN solution (40mL) containing copper chloride (725mg) and tBuONO (0.51mL). This mixture was stirred for 3 hours at room temperature, followed by addition of water and extraction with ethyl acetate. The extract was then washed with water and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20: 1). This gave the desired product as a pale yellow oil (1.10g).

<Reference Example 184>

Benzyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]dihydrocinnamate

[0105]

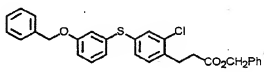


[0106] The compound of Reference Example 169 (840mg) was dissolved in methylene chloride (20mL). While the solution was stirred at 0°C, a 1mol/L methylene chloride solution of tribromoboron (3.42mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Subsequently, ice water was added, and the mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to give 4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamic acid as a pale brown powder (750mg). The resulting powder was dissolved in DMF (50mL). To this solution, potassium carbonate (1.04g) and benzyl bromide (0.602mL) were added and the mixture was stirred at room temperature for 8 hours. Subsequently, the reaction mixture was poured into ice water, and the mixture was extracted with ethyl acetate and was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a brown oil.

<Reference Example 185>

Benzyl 4'-(3-benzyloxyphenylthio)-2'-chlorodihydrocinnamate

[0107]

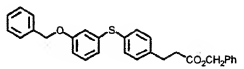


[0108] Using the compound of Reference Example 177, the reaction was carried out in the same manner as in Reference Example 184 to give the desired product as a yellow oil.

<Reference Example 186>

Benzyl 4'-(3-benzyloxyphenylthio)-dihydrocinnamate

[0109]

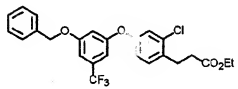


[0110] Using the compound of Reference Example 178, the reaction was carried out in the same manner as in Reference Example 184 to give the desired product as a yellow oil.

<Reference Example 187>

Ethyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]-2'-chlorodihydrocinnamate

[0111]

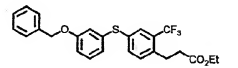


[0112] In the same manner as in Reference Example 184, the compound of Reference Example 142 was reacted to give 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamic acid. This cinnamic acid (1.47g) was dissolved in ethanol (10mL). While this solution was stirred at 0°C, thionyl chloride (3mL) was added dropwise. The mixture was stirred for 2 hours while kept at this temperature. Subsequently, the solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1 and then 6:1) to give ethyl 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate as a colorless oil (1.38g). In the same manner as in Reference Example 184, the resulting ester was converted into a benzyl ether using potassium carbonate and benzyl bromide. This gave the desired product as a colorless oil.

<Reference Example 188>

Ethyl 4'-(3-benzyloxyphenylthio)-2'-trifluoromethyldihydrocinnamate

[0113]

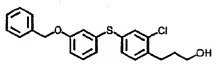


[0114] Using the compound of Reference Example 179, the reaction was carried out in the same manner as in Reference Example 187 to give the desired product as a colorless oil.

<Reference Example 189>

4'-[(3-benzyloxy)phenylthio]-2'-chlorodihydrocinnamyl alcohol

[0115]

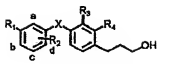


[0116] The compound of Reference Example 185 (7.40g) was dissolved in THF (100mL). While this solution was stirred at 0°C, lithium aluminum hydride (500mg) was added. After 10min, a 20% aqueous solution of NaOH was added and the crystallized insoluble inorganic residue was removed by filtration through Celite. The filtrate was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired product as a colorless oil (6.37g).

<Reference Examples 190 through 251>

[0117] In a similar manner to Reference Example 189, the compounds of Reference Examples 122 through 141, 143 through 168, 170 through 177 and 180 through 188 were used to synthesize the compounds shown in Table4 below.

Table 4

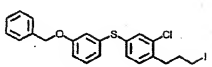


Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
190	Cl	c-Cl	H	Cl	O	221	i-PrO	c-iPr	H	Cl	O
191	t-Bu	H	H	H	O	222	i-PrO	c-iPr	H	H	O
192	Me	H	H	H	O	223	PhO	H	H	Cl	O
193	i-Pr	c-i-Pr	H	Cl	O	224	$PhCH_2O$	H	H	H	O
194	C_6H_{11}	H	H	H	O	225	$PhCH_2O$	H	H	Br	O
195	C_7H_{15}	H	H	H	O	226	$PhCH_2O$	H	H	SMe	O
196	CF_3	H	H	H	O	227	$PhCH_2O$	H	H	Me	O
197	CF_3	H	OMe	H	O	228	$PhCH_2O$	H	H	Et	O
198	CF_3	H	H	OMe	O	229	$PhCH_2O$	c-Cl	H	Cl	O
199	CF_3	H	CF_3	H	O	230	$PhCH_2O$	H	H	CF_3	O
200	CF_3	H	H	CF_3	O	231	$PhCH_2O$	H	H	Ph	O
201	CF_3	c-CF_3	H	H	O	232	$PhCH_2O$	c-$PhCH_2O$	H	Cl	O
202	CF_3	c-CF_3	H	Cl	O	233	$PhCH_2O$	c-$PhCH_2O$	H	H	O
203	CF_3	b-Cl	H	H	O	234	$PhCH_2O$	c-$PhCH_2O$	H	i-Pr	O
204	CF3	a-Cl	H	H	O	235	$PhCH_2O$	c-CF_3	H	H	O
205	CF3	d-Cl	H	H	O	236	$PhCH_2S$	H	H	H	O
206	CF_3	c-$PhCH_2O$	H	Cl	O	237	$PhCH_2S$	H	H	Cl	O
207	$Ph(CH_2)_2$	H	H	Cl	O	238	Cl	H	H	H	S
208	$Ph(CH_2)_2$	H	H	CF_3	O	239	CF_3	c-CF_3	H	Cl	S
209	$Ph(CH_2)_2$	c-CF_3	H	H	O	240	CF_3	c-Me	H	H	S
210	$Ph(CH_2)_2$	c-CF_3	H	Cl	O	241	CF_3	H	H	H	S
211	$Ph(CH_2)_2$	c-$Ph(CH_2)_3$	H	H	O	242	CF_3	H	H	CF_3	S
212	$Ph(CH_2)_2$	c-$Ph(CH_2)_3$	H	CF_3	O	243	MeO	H	H	Cl	S
213	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	Cl	O	244	$PhCH_2O$	H	H	H	S
214	CF_3	H	H	F	O	245	$PhCH_2O$	H	H	CF_3	S
215	$PhCH_2O$	H	H	F	O	246	i-Bu	H	H	H	O
216	CF_3	H	H	Cl	S	247	$PhOCH_2$	H	H	H	O
217	Et	H	H	H	O	248	CF_3	c-Cl	H	H	O
218	CF_3	H	H	$PhCH_2O$	O	249	MeS	H	H	H	O
219	CF_3	H	Cl	H	O	250	$PhCH_2O$	H	H	Cl	O
220	CF_3	H	H	Cl	O	251	$PhCH_2O$	H	H	i-Pr	O

<Reference Example 252>

4'-(3-benzyloxyphenylthio)-2'-chloro-dihydrocinnamyl iodide

[0118]

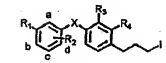


[0119] The compound of Reference Example 189 (1.38g) was dissolved in THF (20mL). While this solution was stirred at 0°C, imidazole (545mg), triphenylphosphine (2.10g) and iodine (2.00g) were added. The mixture was stirred 2 hours at this temperature and subsequent 1.5 hours at room temperature, and additional imidazole (160mg), triphenyl phosphine (600mg) and iodine (500mg) were added. The mixture was stirred overnight, followed by the addition of water and then sodium thiosulfate. The reaction mixture was then extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 50:1) to give the desired product as a colorless oil (1.55g).

<Reference Examples 253 through 314>

[0120] In a similar manner to Reference Example 252, the compounds of Reference Examples 190 through 251 were used to synthesize the compounds shown in Table 5 below.

Table 5

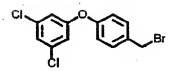


Reference Examples	R1	R2	R3	R4	X	Reference Examples	R1	R2	R3	R4	X
253	Cl	o-Cl	H	Cl	O	284	i-PrO	o-iPr	H	Cl	O
254	t-Bu	H	H	H	O	285	i-PrO	o-iPr	H	H	O
255	Me	H	H	H	O	286	PhO	H	H	Cl	O
256	i-Pr	o-i-Pr	H	Cl	O	287	$PhCH_2O$	H	H	H	O
257	C_6H_{11}	H	H	H	O	288	$PhCH_2O$	H	H	Br	O
258	C_7H_{15}	H	H	H	O	289	$PhCH_2O$	H	H	SMe	O
259	CF_3	H	H	H	O	290	$PhCH_2O$	H	H	Me	O
260	CF_3	H	OMe	H	O	291	$PhCH_2O$	H	H	Et	O
261	CF_3	H	H	OMe	O	292	$PhCH_2O$	o-Cl	H	Cl	O
262	CF_3	H	CF_3	H	O	293	$PhCH_2O$	H	H	CF_3	O
263	CF_3	H	H	CF_3	O	294	$PhCH_2O$	H	H	Ph	O
264	CF_3	o-CF_3	H	H	O	295	$PhCH_2O$	o-$PhCH_2O$	H	Cl	O
265	CF_3	o-CF_3	H	Cl	O	296	$PhCH_2O$	o-$PhCH_2O$	H	H	O
266	CF_3	b-Cl	H	H	O	297	$PhCH_2O$	o-$PhCH_2O$	H	i-Pr	O
267	CF3	a-Cl	H	H	O	298	$PhCH_2O$	o-CF_3	H	H	O
268	CF3	d-Cl	H	H	O	299	$PhCH_2S$	H	H	H	O
269	CF_3	o-$PhCH_2O$	H	Cl	O	300	$PhCH_2S$	H	H	Cl	O
270	$Ph(CH_2)_2$	H	H	Cl	O	301	Cl	H	H	H	S
271	$Ph(CH_2)_2$	H	H	CF_3	O	302	CF_3	o-CF_3	H	Cl	S
272	$Ph(CH_2)_2$	o-CF_3	H	H	O	303	CF_3	o-Me	H	H	S
273	$Ph(CH_2)_2$	o-CF_3	H	Cl	O	304	CF_3	H	H	H	S
274	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	H	O	305	CF_3	H	H	CF_3	S
275	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	CF_3	O	306	MeO	H	H	Cl	S
276	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	Cl	O	307	$PhCH_2O$	H	H	H	S
277	CF_3	H	H	F	O	308	$PhCH_2O$	H	H	CF_3	S
278	$PhCH_2O$	H	H	F	O	309	i-Bu	H	H	H	O
279	CF_3	H	H	Cl	S	310	$PhOCH_2$	H	H	H	O
280	Et	H	H	H	O	311	CF_3	o-Cl	H	H	O
281	CF_3	H	H	$PhCH_2O$	O	312	MeS	H	H	H	O
282	CF_3	H	Cl	H	O	313	$PhCH_2O$	H	H	Cl	O
283	CF_3	H	H	Cl	O	314	$PhCH_2O$	H	H	i-Pr	O

<Reference Example 315>

4-(3,5-dichlorophenoxy)benzyl bromide

[0121]

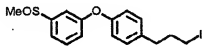


[0122] Using 3,5-dichlorophenol and 4-fluorobenzaldehyde, the reaction was carried out in the same manner as in Reference Example 1 to obtain 4-(3,5-dichlorophenoxy)benzaldehyde. Subsequently, the same procedure as in Reference Example 189 was followed using sodium borohydride in place of the lithium aluminum hydride. This gave 4-(3,5-dichlorophenoxy)benzyl alcohol. The resulting alcohol (2.03g), along with carbon tetrabromide (2.75g), was dissolved in methylene chloride (30mL). While this solution was stirred at 0°C, triphenylphosphine (2.17g) was added. The mixture was stirred at 0°C for 1 hour and at room temperature for the subsequent 30min. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20 : 1) to give the desirec product as a colorless oil (3.12g).

<Reference Example 316>

1-iodopropyl-4-[(3-methanesulfinyl)phenoxy]benzene

[0123]

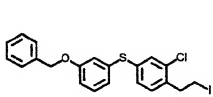


[0124] The compound of Reference Example 312 (1.80g) was dissolved in methylene chloride (30mL). While this solution was stirred at 0°C, m-chlorobenzoic acid (770mg) was added in small portions. The mixture was stirred at this temperature for 1 hour and at room temperature for the subsequent 24 hours. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with a saturated aqueous solution of sodium carbonate and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 2:1 and then 1:2) to give the desired product as a yellow oil (1.29g).

<Reference Example 317>

4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl iodide

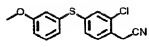
[0125]



<Reference Example 317-1>

2'-chloro-4'-(3-methoxyphenylthio)benzyl cyanide

[0126]

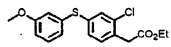


[0127] The compound of Reference Example 53 was treated in the same manner as in Reference Example 189 to obtain an alcohol. The alcohol (5.64g) was dissolved in methylene chloride (100mL) and phosphorus tribromide (2.25mL) was added dropwise. Following stirring at room temperature for 1 hour, ice water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and an aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation to obtain a pale yellow oil. The oil and potassium cyanide (1.56g) were dissolved in a mixture of DMSO (25mL) and water (10mL) and the solution was stirred at 90°C for 5 hours. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10 : 1) to give the desired cyano-product as a pale yellow oil (3.81g).

<Reference Example 317-2>

Ethyl 2'-chloro-4'-(3-methoxyphenylthio)phenylacetate

[0128]



[0129] The cyano-product (3.81g) and potassium hydroxide (3.68g) were added to a mixture of ethanol (80mL) and water (10mL), and the solution was refluxed for 6 hours. Subsequently, the solution was allowed to cool and the insoluble material was removed by filtration. The filtrate was neutralized with diluted hydrochloric acid. This mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and ethanol (50mL) and thionyl chloride (2mL) were added to the resulting residue. This mixture was stirred at room temperature for 1 hour and the solvent was removed by distillation. The resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10:1) to give the ethyl ester product as a colorless oil (3.89g).

<Reference Example 317-3>

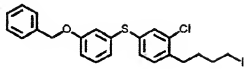
4'-(3-benzyloxyphenylthio)-2'-chlorophenethyl Iodide

[0130] The ethyl ester was reacted in the same manner as in Reference Example 187 to obtain ethyl 4'-(3-benzyloxyphenylthio)-2'-chlorophenyl-acetate. The product was reduced as in Reference Example 189 to obtain an alcohol, which in turn was reacted in the same manner as in Reference Example 252 to give the desired product as a colorless oil.

<Reference Example 318>

1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene

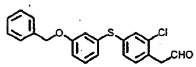
[0131]



<Reference Example 318-1>

4-(3-benzyloxyphenylthio)-2-chlorophenethyl aldehyde

[0132]

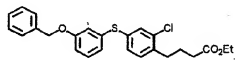


[0133] Ethyl 4'-(3-benzyloxyphenylthio)-2'-chlorophenylacetate obtained in Reference Example 317-3 was subjected to alkali-hydrolysis. The resulting product was condensed with N, O-dimethylhydroxylamine to form an amide product, which in turn was reduced in the same manner as in Reference Example 189 to give the desired aldehyde product as a yellow oil.

<Reference Example 318-2>

Ethyl 4-[(3-benzyloxyphenylthio)-2-chlorophenyl]butyrate

[0134]



[0135] The compound of Reference Example 318-1 was reacted in the same manner as in Reference Example 50 and the unsaturated bonds of the resulting product were reduced in the same manner as in Reference Example 122 to give the desired ethyl butyrate derivative.

<Reference Example 318-3>

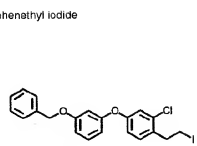
1-(3-benzyloxyphenylthio)-3-chloro-4-iodobutylbenzene

[0136] The compound of Reference Example 318-2 was reacted in the same manner as in Reference Example 189 to obtain an alcohol product, which in turn was reacted in the same manner as in Reference Example 252 to give the desired product as a colorless oil.

<Reference Example 319>

4'-[(3-benzyloxy)phenoxy]-2'-chlorophenathyl iodide

[0137]

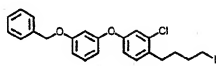


[0138] The compound of Reference Example 56 was reacted in the same manner as in Reference Example 317 to obtain the desired product as a yellow oil.

<Reference Example 320>

4-[(3-benzyloxy)phenoxy]-2-chloro-1-iodobutylbenzene

[0139]

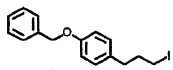


[0140] The compound of Reference Example 56 was reacted in the same manner as in Reference Example 318 to obtain the desired product as a pale yellow oil.

<Reference Example 321>

4'-benzyloxydihydrocinnamyl iodide

[0141]

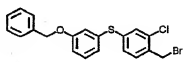


[0142] 4'-benzyloxydihydrocinnamyl alcohol was reacted in the same manner as in Reference Example 252 to obtain the desired product as a yellow powder.

<Reference Example 322>

4'-(3-benzyloxyphenylthio)-2'-chlorobenzyl bromide

[0143]

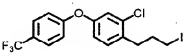


[0144] In place of 2-chloro-4-fluorobenzaldehyde, 2-chloro-4-fluorobenzonitrile was reacted in the same manner as in Reference Example 1 to obtain 2-chloro-4-(3-methoxyphenylthio)benzonitrile. Following the same procedure as in Reference Example 317-2, this product was hydrolyzed and, then, following the same procedure as in Reference Example 187, the methoxy group was decomposed and esterified to convert the product into a benzyl ether. The product was then reacted in the same manner as in Reference Example 189 to be converted into an alcohol. Subsequently, the product was reacted with carbon tetrabromide in the same manner as in Reference Example 315 to obtain the desired product as a colorless oil.

<Reference Example 323>

2'-chloro-4'-(4-trifluoromethylphenoxy)dihydrocinnamyl iodide

[0145]

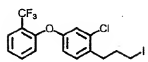


[0146] Using p-trifluoromethylphenol, the reaction was carried out in the same manner as in Reference Example 1 to obtain an aldehyde. Following the same procedure as in Reference Example 60, the aldehyde was subjected to Horner-Emmons reaction. Subsequently, following the same procedure as in Reference Example 123, the resulting product was reduced and, then, following the same procedure as in Reference Example 189, the reduced product was converted into an alcohol. Subsequently, the alcohol was iodized in the same manner as in Reference Example 252 to give the desired product as a colorless oil.
MS(EI+): 440 ([M]+).
^{1}H-NMR (400MHz, $CDCl_3$) δ 2.12-2.19 (2H, m), 2.85(2H, t, J=7.3Hz), 3.21(2H, t, J=7.3Hz), 6.90(1H, dd, J=2.5, 8.6Hz), 7.04-7.08(3H, m), 7.23-7.27(1H, m), 7.60(2H, d, J=8.6Hz).

<Reference Example 324>

2'-chloro-4'-(2-trifluoromethylphenoxy)dihydrocinnamyl iodide

[0147]

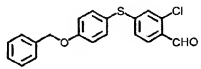


[0148] Using o-trifluoromethylphenol, the reaction was carried out in the same manner as in Reference Example 232 to obtain the desired product as a colorless oil.
MS (EI+) : 440 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 2.11-2.18 (2H, m), 2.83(2H, t, J=7.3Hz), 3.21(2H, t, J=7.3Hz), 6.88(1H, dd, J=2.5, 8.6Hz), 6.96(1H, d, J=8.6Hz), 7.04(1H, d, J=2.5Hz) 7.18-7.26(2H, m), 7.49(1H, t, J=8.6Hz), 7.68(1H, d, J=8.0Hz).

<Reference Example 325>

4-(4-benzyloxyphenylthio)-2-chlorobenzaldehyde

[0149]

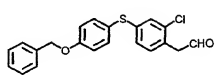


[0150] p-hydroxythiophenol (2.12g) was dissolved in N,N-dimethylformamide (40mL). To this solution, 2-chloro-4-fluorobenzaldehyde (2.66g) and potassium carbonate (4.64g) were added and the mixture was stirred for 2 hours at 50°C. Subsequently, benzyl bromide (4.00mL) was added and the mixture was stirred for 1.5 hours at 50°C and then for 2.5 hours at 70°C. The reaction mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. Following addition of water, the solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 10: 1). This gave the desired product as a colorless solid (5.70g).
^{1}H-NMR (400MHz, $CDCl_3$) δ 5. 12 (2H, s), 6.96-7.03(3H, m), 7.06 (2H, m), 7.38-7.50(6H, m), 8.56(1H, d, J=8.6Hz), 10.33(1H, s).

<Reference Example 326>

4'-(4-benzyloxyphenylthio)-2'-chlorophenethylaldehyde

[0151]

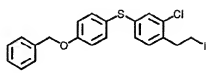


[0152] To an ice-cold tetrahydrofuran solution (160mL) of (Methoxymethyl)triphenylphosphonium chloride (8.28g), t-butoxy potassium (2.71g) was added and the mixture was stirred for 1 hour, followed by addition of the compound of Reference Example 325 (5.70g) and 1 hour of stirring. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and the resulting residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 6 : 1). This gave the desired vinyl ether product as a pale yellow oil (6.50g). This product was dissolved in tetrahydrofuran (90mL). To this solution, a 6mol/L aqueous solution of hydrochloric acid (60mL) was added and the mixture was stirred for 5 hours at 60°C. Subsequently, the reaction mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. Following addition of water, the solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 9 : 1). This gave the desired product as a colorless powder (4.48g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 3.77(2H, d, J=1.8Hz), 5.09(2H, s), 6.97-7.04(3H, m), 7.05-7.10(1H, m), 7.15(1H, d, J=1.8Hz), 7.32-7.46(7H, m), 9.72(1H, t, J=1.8Hz).

<Reference Example 327>

4'-(4-benzyloxyphenylthio)-2'-chlorophenethyl iodide

[0153]

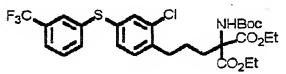


[0154] Following the same procedure as in Reference Example 189, the compound of Example 326 was converted into an alcohol. Then, using the same procedure as in Reference Example 252 this alcohol was iodized to give the desired product as a pale yellow oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 3.22(2H, t, J=7.3Hz), 3.30(2H, t, J=7.3Hz), 5.09(2H, s) 6.96-7.02(3H, m), 7.09(2H, d, J=7.9Hz), 7.33-7.45(7H, m).

<Example 1>

Ethyl 2-t-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]-2-etoxycarbonylpentanoate

[0155]

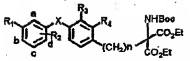


[0156] At room temperature and under a stream of argon gas, sodium t-butoxide (490mg) was added to diethyl 2-t-butoxycarbonylaminomalonate (1.3mL) in a mixture of THF (35mL) and DMF (4mL). This mixture was stirred for 20min at 80°C and was allowed to cool to room temperature. To the cooled mixture, a THF solution (5mL) of the compound of Reference Example 279 (1.55g) was added dropwise. The resulting mixture was refluxed for 5 hours, was poured into ice water, and was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate.
The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 5 : 1) to give the desired product as a colorless oil (1.87g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.22-1.38(6H, m), 1.42(9H, s), 1.45-1.53(2H, m), 2.37(2H, br), 2.74(2H, t, J=7.8Hz), 4.23 (4H, m), 5.94 (1H, s), 7.18-7.21(2H, m), 7.36-7.56(5H, m).

<Examples 2 through 67>

[0157] In a similar manner to Example 1, the halogen derivatives of respective Reference Examples were used to synthesize the compounds shown in Tables 6 and 7 below.

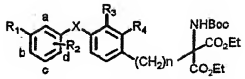
Table 6



Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)
2	Cl	o-Cl	H	Cl	O	3	Colorless oil	74
3	t-Bu	H	H	H	O	3	Colorless oil	64
4	CF_3	H	H	H	O	3	Colorless oil	100
5	CF_3	H	OMe	H	O	3	Colorless oil	100
6	CF_3	H	H	OMe	O	3	Colorless oil	100
7	CF_3	H	CF_3	H	O	3	Colorless oil	100
8	CF_3	H	H	CF_3	O	3	Colorless oil	92
9	CF_3	o-CF_3	H	H	O	3	Yellow oil	47
10	CF_3	o-CF_3	H	Cl	O	3	Colorless oil	89
11	CF_3	b-Cl	H	H	O	3	Colorless oil	94
12	CF_3	o-$PhCH_2O$	H	Cl	O	3	Colorless oil	91
13	$Ph(CH_2)_2$	H	H	Cl	O	3	Colorless oil	83
14	$Ph(CH_2)_2$	H	H	CF_3	O	3	Colorless oil	90
15	$Ph(CH_2)_2$	o-CF_3	H	H	O	3	Colorless oil	97
16	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	H	O	3	Colorless oil	95
17	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	CF_3	O	3	Colorless oil	100
18	$Ph(CH_2)_2$	o-$Ph(CH_2)_2$	H	Cl	O	3	Colorless oil	98
19	i-PrO	o-iPr	H	Cl	O	3	Colorless oil	100
20	PhO	H	H	Cl	O	3	Colorless oil	92
21	$PhCH_2O$	H	H	H	O	3	Colorless oil	96
22	$PhCH_2O$	H	H	Br	O	3	Colorless oil	100
23	$PhCH_2O$	H	H	SMe	O	3	Colorless oil	-
24	$PhCH_2O$	H	H	Me	O	3	Colorless oil	100
25	$PhCH_2O$	H	H	Et	O	3	Colorless oil	72
26	$PhCH_2O$	H	H	Cl	S	2	Pale yellow oil	100
27	$PhCH_2O$	H	H	Cl	S	3	Colorless oil	100
28	$PhCH_2O$	H	H	Cl	S	4	Colorless oil	100
29	$PhCH_2O$	o-CF_3	H	H	O	3	Colorless oil	99
30	Cl	H	H	H	S	3	Colorless oil	82
31	CF_3	o-CF_3	H	Cl	S	3	Colorless oil	68
32	Et	H	H	H	O	3	Colorless oil	100
33	SOMe	H	H	H	O	3	Colorless oil	100
34	Cl	o-Cl	H	H	O	1	Colorless oil	56
35	CF_3	H	H	$PhCH_2O$	O	3	Colorless oil	100
36	$PhCH_2O$	H	H	Cl	O	3	Colorless oil	100
37	CF_3	H	Cl	H	O	3	Colorless oil	100
38	CF_3	H	H	Cl	O	3	Colorless oil	100
39	PhCH2O	H	H	F	O	3	Colorless oil	100
40	CF_3	a-Cl	H	H	O	3	Colorless oil	100

- Yield is shown in Tables 8-10 in association with the subsequent step.

Table 7



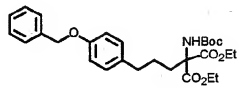
Examples	R1	R2	R3	R4	X	n	Characteristics	Yield (%)
41	CF3	c-Cl	H	H	O	3	Pale yellow oil	41
42	CF_3	d-Cl	H	H	O	3	Pale yellow oil	72
43	$Ph(CH_2)_2$	c-CF_3	H	Cl	O	3	Colorless oil	93
44	$PhCH_2O$	H	H	Cl	O	2	Colorless oil	-
45	$PhCH_2O$	H	H	Cl	O	4	Colorless oil	-
46	CF_3	H	H	F	O	3	Colorless oil	100
47	$PhCH_2O$	c-$PhCH_2O$	H	H	O	3	Colorless oil	-
48	$PhCH_2O$	c-$PhCH_2O$	H	Cl	O	3	Colorless oil	-
49	$PhCH_2O$	c-Cl	H	Cl	O	3	Colorless oil	100
50	$PhCH_2O$	H	H	CF_3	O	3	Colorless oil	100
51	$PhCH_2O$	H	H	Ph	O	3	Colorless oil	-
52	MeS	H	H	H	O	3	Colorless oil	83
53	n-C_5H_{11}	H	H	H	O	3	Colorless oil	86
54	c-C_7H_{15}	H	H	H	O	3	Colorless oil	88
55	iPr	c-iPrO	H	H	O	3	Colorless oil	95
56	iPr	c-iPr	H	Cl	O	3	Colorless oil	66
57	$PhCH_2S$	H	H	H	O	3	Colorless oil	-
58	$PhCH_2S$	H	H	Cl	O	3	Colorless oil	-
59	i-Bu	H	H	H	O	3	Colorless oil	76
60	$PhOCH_2$	H	H	H	O	3	Colorless oil	100
61	$PhCH_2O$	H	H	i-Pr	O	3	Colorless oil	-
62	CF_3	H	H	H	S	3	Colorless oil	90
63	CF_3	H	H	CF_3	S	3	Pale yellow oil	53
64	CF_3	c-Me	H	H	S	3	Colorless oil	100
65	MeO	H	H	Cl	S	3	Colorless oil	87
66	$PhCH_2O$	H	H	H	S	3	Colorless oil	-
67	$PhCH_2O$	H	H	CF_3	S	3	Colorless oil	100
68	$PhCH_2O$	H	H	Cl	S	1	Colorless oil	100

- Yield is shown in Tables 8-10 in association with the subsequent step.

<Example 69>

Ethyl 5-[(4-benzyloxy)phenyl]-2-t-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0158]

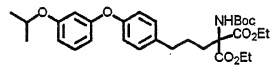


[0159] The compound of Reference Example 321 was reacted in the same manner as in Example 1 to give the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.22(6H, t, J=7.1Hz), 1.42(9H, s), 1.44-1.47(2H, m), 2.31(2H, br s), 2.57(2H, t, J=7.6Hz), 4.11-4.27(4H, m), 5.03(2H, s), 5.92 (1H, br s), 6.88(2H, d, J=8.8Hz), 7.06(2H, d, J=8.8Hz), 7.29-7.43(5H, m).

<Example 70>

Ethyl 2-t-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-isopropoxyphenoxy)phenyl]pentanoate

[0160]

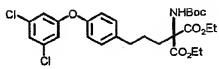


[0161] The compound of Example 69 was reduced in the same manner as in Reference Example 123. The resulting phenol product (850mg) was dissolved in DMF (20mL). To this solution, 2-iodopropane (0.2mL) and potassium carbonate (500mg) were added and the mixture was stirred for 4 hours at 60°C. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 4 : 1) to give the desired product as a colorless oil (760mg).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.31(6H, d, J=5.9Hz), 1.42(9H, s), 1.45-1.52(2H, m), 2.34(2H, br), 2.61(2H, t, J=7.8Hz), 4.17-4.27(4H, m), 4.50(1H, heptet, 5.9Hz), 5.94(1H, br s), 6.50-6.53 (2H, m), 6.59-6 62 (1H, m), 6.92 (2H, d, J=8.8Hz), 7.10(2H, d, J=8.8Hz), 7.18(1H, t, J=8.8Hz).

<Example 71>

Ethyl 2-t-butoxycarbonylamino-5-[4-(3,5-dichlorophenoxy)phenyl]-2-ethoxycarbonylpentanoate

[0162]

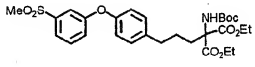


[0163] The compound of Example 69 was reduced in the same manner as in Reference Example 123. The resulting phenol product (1.27g), along with 3,5-dichlorophenylboric acid (1.18g), was dissolved in methylene chloride (30mL). While this solution was being stirred, copper acetate (676mg) and triethylamine (0.86mL) were added. After 16 hours and a further 8 hours later, the same amount of additional copper acetate was added and the mixture was stirred for the subsequent 40 hours. Subsequently, the insoluble material was removed by filtration. The filtrate was poured into water and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 20 : 1) to give the desired product as a pale blue oil (333mg).

<Example 72>

Ethyl 2-t-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-methanesulfonylphenoxy)phenyl]pentanoate

[0164]

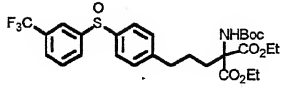


[0165] The compound of Example 33 (1.00g) was dissolved in methylene chloride (30mL). To this solution, m-chloroperbenzoic acid (610mg) was added and the mixture was stirred for 6 hours at room temperature. Following addition of water, the mixture was extracted with ethyl acetate and the extract was washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1 : 1) to give the desired product as a colorless oil (610mg).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.42(9H, s), 1.47-1.56(2H, m), 2.34(2H, br), 2.64(2H, t, J=7.8Hz), 3.04(3H; s), 4.18-4.26(4H, m), 5.95(1H br), 6.95(2H, d, J=8.8Hz), 7.17(2H, t, J=8.8Hz), 7.20-7.30(3H, m), 7.47-7.52 (2H, m), 7. 62 (1H, d, J=8.8Hz).

<Example 73>

Ethyl 2-t-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-trifluoromethylphenylsulfinyl)]phenylpentanoate

[0166]



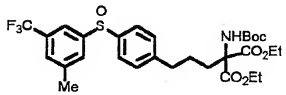
[0167] The compound of Example 62 (1.50g) was dissolved in methylene chloride (80mL). While this solution was stirred at 0°C, m-chloroperbenzoic acid (450mg) was added in small portions. The mixture was then stirred for 1 hour at this temperature and 2 hours at room temperature. Subsequently, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1 : 1) to give the desired product as a yellow oil (1.10g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.21(6H, m), 1.40(9H, s), 1.44-1.52(2H, m), 2.30(2H, br), 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.91(1H, br), 7.27(2H, d, J=8.3Hz), 7.56(2H, d, J=8.3Hz), 7.59(1H, t, J=8.3Hz), 7.69(1H, d, J=8.3Hz),

7.78(1H, d, J=8.3Hz), 7.95(1H, s).

<Example 74>

Ethyl 2-t-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-trifluoromethyl-5-methylphenylsulfinyl)]phenylpentanoate

[0168]

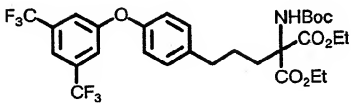


[0169] In a similar manner to Example 73, the compound of Example 64 was used to obtain the desired product as a colorless oil.
FABMS:600 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18-1.22(6H, m), 1.41(9H, s), 1.46-1.50(2H, m), 2.31(2H, br), 2.45(3H, s) 2.66(2H, t, J=7.3Hz), 4.14-4.22(4H, m), 5.92(1H, br s), 7.27(2H, d, J=7.8Hz), 7.48(1H, s), 7.55(2H, d, J=7.8Hz), 7.62(1H, s), 7.70 (1H, s).

<Example 75> Alternative process for synthesizing the compound of Example 9

Ethyl 5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]-2-t-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0170]

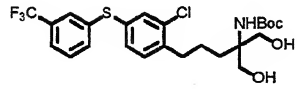


[0171] In a similar manner to Reference Example 123, the compound of Example 69 was reduced and, then, in a similar manner to Example 71, the resulting phenol was reacted with 3,5-bis(trifluoromethyl)phenylboric acid to give the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) 5 1.24(6H, t, J=7.3Hz), 1.43(9H, s), 1.47-1.58(4H, m), 2.36(2H, br s), 2.66(2H, t, J=7.3Hz), 4.18-4.26(4H, m), 5.96 (1H, br s), 6.96(2H, d, J=8.3Hz), 7.20(2H, d, J=8.3Hz), 7.36(2H, s), 7.55 (1H. s).

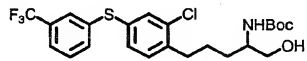
<Examples 76 and 77>

2-t-butoxycarbonylamino-2-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]propyl-1,3-propanediol (Example 76);

[0172]



and 2-t-butoxycarbonylamino-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]pentane-1-ol (Example 77)



[0173] The compound of Example 1 (1.87g) was dissolved in THF (30mL). While this solution was stirred at 0°C, lithium borohydride (675mg) was added. Ethanol (5mL) was added and the mixture was allowed to gradually warm to room temperature while being stirred overnight. Subsequently, ice water was added to the mixture and the organic solvent was removed under reduced pressure. A 10% aqueous citric acid was added to the residue to adjust the pH to 3, followed by extraction with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1 : 1) to give the diol (1.10g) or the monool (0.27g), each as a colorless oil.

(Compound of Example 76)

[0174] FABMS:520([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ1.43(9H, s), 1.62-1.65(4H, m), 2.72(2H,br), 3.31(2H, br), 3.57-3.62(2H, m), 3.81-3.85(2H, m), 4.93(1H, s), 7.20-7.27(3H, m), 7.38-7.55(4H, m).

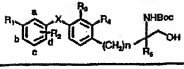
(Compound of Example 77)

[0175] FABMS:490([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ1.44(9H, s), 1.63-1.73(4H, m), 2.72-2.78(2H, m), 3.57(1H, br), 3.68-3.70(2H, m), 4.61(1H, br s), 7.20-7.22(2H, m), 7.39-7.55(5H, m).

<Examples 78 through 184>

[0176] In a similar manner to Example 76, the compounds of 2 through 68 and 70 through 74 were used to synthesize compounds shown in Tables 8 through 10 below.

Table 8



Examples	R1	R2	R3	R4	R5	X	n	Characteristics	Yield (%)
78	Cl	c-Cl	H	Cl	CH_2OH	O	3	Colorless oil	79
79	Cl	c-Cl	H	Cl	H	O	3	Colorless oil	12
80	t-Bu	H	H	H	CH_2OH	O	3	Colorless oil	76
81	t-Bu	H	H	H	H	O	3	Colorless oil	15
82	CF_3	H	H	H	CH_2OH	O	3	Colorless oil	74
83	CF_3	H	H	H	H	O	3	Colorless oil	17
84	CF_3	H	OMe	H	CH_2OH	O	3	Colorless oil	76
85	CF_3	H	OMe	H	H	O	3	Colorless oil	5
86	CF_3	H	H	OMe	CH_2OH	O	3	Colorless oil	45
87	CF_3	H	H	OMe	H	O	3	Colorless oil	17
88	CF_3	H	CF_3	H	CH_2OH	O	3	Colorless oil	68
89	CF_3	H	CF_3	H	H	O	3	Colorless oil	16
90	CF_3	H	H	CF_3	CH_2OH	O	3	Colorless oil	41
91	CF_3	H	H	CF_3	H	O	3	Colorless oil	22
92	CF_3	c-CF_3	H	H	CH_2OH	O	3	Colorless oil	72
93	CF_3	c-CF_3	H	H	H	O	3	Yellow oil	14
94	CF_3	c-CF_3	H	Cl	CH_2OH	O	3	Colorless oil	77
95	CF_3	c-CF_3	H	Cl	H	O	3	Colorless oil	19
96	CF_3	b-Cl	H	H	CH_2OH	O	3	Colorless powder	62
97	CF_3	b-Cl	H	H	H	O	3	Colorless powder	29
98	CF_3	c-$PhCH_2O$	H	Cl	CH_2OH	O	3	Colorless oil	67
99	CF_3	c-$PhCH_2O$	H	Cl	H	O	3	Colorless oil	12
100	$Ph(CH_2)_2$	H	H	Cl	CH_2OH	O	3	Colorless oil	84
101	$Ph(CH_2)_2$	H	H	Cl	H	O	3	Colorless oil	15
102	$Ph(CH_2)_2$	H	H	CF_3	CH_2OH	O	3	Colorless oil	72
103	$Ph(CH_2)_2$	H	H	CF_3	H	O	3	Colorless oil	18
104	$Ph(CH_2)_2$	c-CF_3	H	H	CH_2OH	O	3	Colorless oil	80
105	$Ph(CH_2)_2$	c-CF_3	H	H	H	O	3	Colorless oil	16
106	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	H	CH_2OH	O	3	Colorless oil	71
107	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	H	H	O	3	Colorless oil	11
108	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	CF_3	CH_2OH	O	3	Colorless oil	64
109	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	CF_3	H	O	3	Colorless oil	13
110	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	Cl	CH_2OH	O	3	Colorless oil	61
111	$Ph(CH_2)_2$	c-$Ph(CH_2)_2$	H	Cl	H	O	3	Colorless oil	10
112	i-PrO	c-iPr	H	Cl	CH_2OH	O	3	Colorless oil	82
113	i-PrO	c-iPr	H	Cl	H	O	3	Colorless oil	7
114	PhO	H	H	Cl	CH_2OH	O	3	Colorless oil	76
115	PhO	H	H	Cl	H	O	3	Colorless oil	17
116	$PhCH_2O$	H	H	H	CH_2OH	O	3	Colorless oil	76
117	$PhCH_2O$	H	H	H	H	O	3	Colorless oil	11
118	$PhCH_2O$	H	H	Br	CH_2OH	O	3	Colorless oil	61
119	$PhCH_2O$	H	H	Br	H	O	3	Colorless oil	11
120	$PhCH_2O$	H	H	SMe	CH_2OH	O	3	Colorless oil	(38)
121	$PhCH_2O$	H	H	SMe	H	O	3	Colorless oil	(10)

Numbers in parentheses are cumulative yields from the previous step.

Table 9

Examples	R1	R2	R3	R4	R5	X	n	Characteristics	Yield %
122	$PhCH_2O$	H	H	Me	CH_2OH	O	3	Colorless oil	75
123	$PhCH_2O$	H	H	Me	H	O	3	Colorless oil	11
124	$PhCH_2O$	H	H	Et	CH_2OH	O	3	Colorless oil	61
125	$PhCH_2O$	H	H	Et	H	O	3	Colorless oil	8
126	$PhCH_2O$	H	H	Cl	CH_2OH	S	2	Colorless powder	41
127	$PhCH_2O$	H	H	Cl	H	S	2	Pale yellow oil	11
128	$PhCH_2O$	H	H	Cl	CH_2OH	S	3	Colorless powder	65
128	$PhCH_2O$	H	H	Cl	H	S	3	Colorless oil	28
130	$PhCH_2O$	H	H	Cl	CH_2OH	S	4	Colorless oil	76
131	$PhCH_2O$	H	H	Cl	H	S	4	Colorless oil	15
132	$PhCH_2O$	c-CF_3	H	H	CH_2OH	O	3	Colorless oil	83
133	$PhCH_2O$	c-CF_3	H	H	H	O	3	Colorless oil	10
134	Cl	H	H	H	CH_2OH	S	3	Colorless oil	41
135	Cl	H	H	H	H	S	3	Colorless oil	31
136	CF_3	c-CF_3	H	Cl	CH_2OH	S	3	Colorless amorphous	68
137	CF_3	c-CF_3	H	Cl	H	S	3	Colorless oil	13
138	Et	H	H	H	CH_2OH	O	3	Colorless oil	76
139	Et	H	H	H	H	O	3	Colorless oil	13
140	SOMe	H	H	H	CH_2OH	O	3	Colorless oil	67
141	SOMe	H	H	H	H	O	3	Colorless oil	27
142	Cl	c-Cl	H	H	CH_2OH	O	1	Colorless amorphous	56
143	Cl	c-Cl	H	H	H	O	1	Colorless powder	24
144	CF_3	H	H	$PhCH_2O$	CH_2OH	O	3	Colorless oil	64
145	CF_3	H	H	$PhCH_2O$	H	O	3	Colorless oil	5
148	$PHCH_2O$	H	H	Cl	CH_2OH	O	3	Colorless oil	77
147	$PhCH_2O$	H	H	Cl	H	O	3	Colorless oil	19
148	CF_3	H	Cl	H	CH_2OH	O	3	Colorless oil	58
149	CF_3	H	H	Cl	CH_2OH	O	3	Colorless oil	68
150	$PhCH_2O$	H	H	F	CH_2OH	O	3	Colorless oil	34
151	CF_3	a-Cl	H	N	CH_2OH	O	3	Colorless oil	57
152	CF_3	c-Cl	H	H	CH_2OH	O	3	Colorless oil	51
153	CF_3	d-Cl	H	H	CH_2OH	O	3	Colorless oil	37
154	$Ph(CH_2)_2$	c-CF_3	H	Cl	CH_2OH	O	3	Colorless oil	46
155	$PhCH_2O$	H	H	Cl	CH_2OH	O	2	Colorless powder	(49)
156	$PhCH_2O$	H	H	Cl	CH_2OH	O	4	Colorless oil	(72)
157	CF_3	H	H	F	CH_2OH	O	3	Colorless oil	63
158	$PhCH_2O$	c-$PhCH_2O$	H	H	CH_2OH	O	3	Colorless oil	(45)
159	$PhCH_2O$	c-$PhCH_2O$	H	Cl	CH_2OH	O	3	Colorless oil	(17)
160	$PhCH_2O$	c-Cl	H	Cl	CH_2OH	O	3	Colorless oil	61
161	$PhCH_2O$	H	H	CF_3	CH_2OH	O	3	Colorless oil	83
162	$PhCH_2O$	H	H	Ph	CH_2OH	O	3	Colorless oil	(50)
163	MeS	H	H	H	CH_2OH	O	3	Colorless powder	56
164	n-C_6H_{11}	H	H	H	CH_2OH	O	3	Colorless oil	98
165	c-C_7H_{15}	H	H	H	CH_2OH	O	3	Colorless oil	90
166	IPr	c-iPrO	H	H	CH_2OH	O	3	Colorless oil	72
167	IPr	c-IPr	H	Cl	CH_2OH	O	3	Colorless oil	33
168	$PhCH_2S$	H	H	H	CH_2OH	O	3	Colorless oil	(20)

Table 9 (continued)

Examples	R1	R2	R3	R4	R5	X	n	Characteristics	Yield %
Numbers in parentheses are cumulative yields from the previous step.									

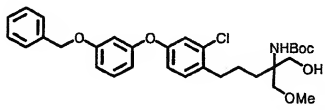
Table 10

Examples	R1	R2	R3	R4	R5	X	n	Characteristics	Yield (%)
169	$PhCH_2S$	H	H	Cl	CH_2OH	O	3	Colorless oil	(11)
170	I-Bu	H	H	H	CH_2OH	O	3	Colorless oil	92
171	$PhOCH_2$	H	H	H	CH_2OH	O	3	Colorless oil	64
172	$PhCH_2O$	H	H	I-Pr	CH_2OH	O	3	Colorless oil	(62)
173	CF_3	H	H	H	CH_2OH	S	3	Colorless powder	89
174	CF_3	H	H	H	CH_2OH	SO	3	Colorless amorphous	71
175	CF_3	H	H	CF_3	CH_2OH	S	3	Colorless oil	51
176	CF_3	c-Me	H	H	CH_2OH	S	3	Colorless powder	81
177	CF_3	c-Me	H	H	CH_2OH	SO	3	Colorless powder	65
178	MeO	H	H	Cl	CH_2OH	S	3	Colorless oil	56
179	$PhCH_2O$	H	H	H	CH_2OH	S	3	Colorless oil	(45)
180	$PhCH_2O$	H	H	CF_3	CH_2OH	S	3	Colorless oil	66
181	Cl	c-Cl	H	H	CH_2OH	O	3	Colorless oil	50
182	Cl	c-Cl	H	H	H	O	3	Colorless oil	13
183	$MeSO_2$	H	H	H	CH_2OH	O	3	Colorless amorphous	78
184	i-PrO	H	H	H	CH_2OH	O	3	Colorless oil	68
Numbers in parentheses are cumulative yields from the previous step.									

<Example 185>

5- [4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethylpentane-1-ol

[0177]



[0178] The compound of Example 146 (720mg) was dissolved in acetonitrile (20mL). To this solution, Ag_2O (1.85g) and MeI (3mL) were added and the mixture was stirred for 7 days at room temperature. Subsequently, the mixture was filtered through Celite and the filtrate was concentrated and purified on a silica gel column chromatography (hexane: ethyl acetate = 3:1). This gave the desired product as a colorless oil (310mg).

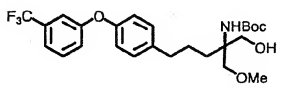
FABMS: 556 ($[M+H]^+$).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.43 (9H, s), 1.48-1.81 (4H, m), 2.68 (2H, t, J=7.8Hz), 3.33(1H, d, J=8.8Hz), 3.36(3H, s), 3.57(1H, d, 8.8Hz), 3.65(2H d, J=6.8Hz), 5.03(2H, s), 5.10(1H. br s), 6.59-6.62(2H, m), 6.74 (1H, dd, J=8.3, 2.4Hz), 6.84 (1H, dd, J=8.3, 2 4Hz), 7.00(1H, d, J=2.4Hz), 7.15(1H, d, J=8.3Hz), 7.23 (1H, t, J=8.3Hz), 7.33-7.42(5H, m).

<Example 186>

2-t-butoxycarbonylamino-2-methoxymethyl-5-[4-(3-trifluoromethylphenoxy)phenyl]pentane-1-ol

[0179]

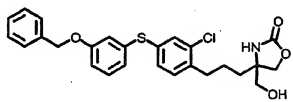


[0180] In a similar manner to Example 185, the compound of Example 82 was reacted to obtain the desired product as a colorless oil.
FABMS: 484 ([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.42(9H, s), 1.48-1.83(4H, m), 2.57-2.65(2H, m), 3.33(1H, d, J=8.8Hz), 3.37(3H, s), 3.58 (1H. d, 8.8Hz), 3.62(2H. br s), 5.07(1H, br s), 6.94(2H. d, J=6.4Hz), 7.10-7.21(4H. m),7.30 (1H, d, J=7.8Hz), 7.40(1H, t J=7.8Hz).

<Example 187>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-hydroxymethyl-2-oxazolidinone

[0181]

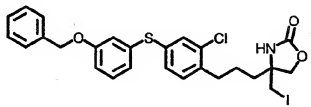


[0182] The compound of Example 128 (3.30g) was dissolved in THF (60mL). While this solution was kept at 0°C, 60% sodium hydride (600mg) was added and the mixture was stirred for 2,4 hours at room temperature. Subsequently, ice water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 1 : 1 then 100% ethyl acetate) to give the desired product as a pale yellow oil (2.37g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.63-1.72(4H, m), 2.74(2H, t, J=6.8Hz), 3.51(1H, d, J=11.2Hz), 3.58(1H, d, J=11.2Hz), 4.09(1H, d, J=8.8Hz), 4.24(1H, d, J=8.8Hz), 5.02(2H, s), 5.28(1H. br s), 6.87-6.90(1H, m), 6.94-7.00(2H. m), 7.09-7.16 (2H. m), 7.22-7.52(7H, m) .

<Example 188>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-iodomethyl-2-oxazolidinone

[0183]

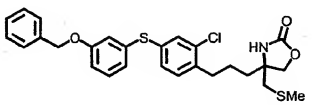


[0184] The compound of Example 187 (2.37g) was dissolved in pyridine (30mL). To this solution, p-toluenesulfonylchloride (1.33g) was added and the mixture was stirred for 24 hours at room temperature and a further 5 hours at 60°C. Following addition of water, the mixture was extracted with ethyl acetate. The extract was then washed sequentially with water, diluted hydrochloric acid and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel chromatography (hexane : ethyl acetate = 1 : 1) to obtain a sulfonic acid ester as a colorless oil (2.14g). The sulfonic acid ester (2.14g) was dissolved in acetone (20mL), followed by addition of sodium iodide (2.55g) and refluxing for 10 hours. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel chromatography (hexane : ethyl acetate = 1 : 1) to give the desired product as a colorless oil (1.47g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.59-1.65(2H, m), 1.83-1.89(2H, m), 2.75(2H, t, J=7.8Hz), 3.31(2H, s), 4.19 (1H, d, J=9.3Hz), 4.21(1H, d, J=9.3Hz), 5.02(2H, s), 5.13(1H, br s), 6.88(1H, dd, J=7.8, 2.0Hz), 6.94-7.00(2H, m), 7.11 (1H, d, J=7.8Hz), 7.16 (1H, dd, J=7.8, 2.0Hz), 7.22-7.41(7H, m).

<Example 189>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-methylthiomethyl-2-oxazolidinone

[0185]

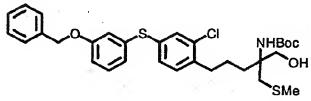


[0186] The compound of Example 188 (1.47g) was dissolved in THF (30mL). To this solution, NaSMe (210mg) was added and the mixture was stirred for 2 hours at room temperature. Following addition of water, the mixture was extracted with ethyl acetate. The extract was then washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure to give the desired product as a colorless oil (1.27g).
FABMS: 514 ([M+H]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.62-1.77(4H, m), 2.17 (3H, s), 2.68 (1H, d, J=13.2Hz), 2.74(2H, t, J=7.3Hz), 2.78(1H. d, J=13.2Hz), 4.15 (1H, d, J=9.0Hz), 4.20(1H, d, J=9.0Hz). 5.03(2H, s), 5.22(1H, br s), 6.87-6.90(1H, m), 6.93-6.97(2H, m), 7.10-7.17(2H, m), 7.22-7.41(7H, m).

<Example 190>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2- t-butoxycarbonylamino-2-methylthiomethylpentane-1-ol

[0187]



[0188] The compound of Example 189 (1.27g) was dissolved in acetonitrile (20mL). To this solution, Boc_2O (1.09g) and dimethylaminopyridine (100mg) were added and the mixture was stirred for 30min at room temperature. The solvent was removed under reduced pressure and the residue was purified on a silica gel chlomatography (hexane : ethyl acetate = 4 : 1) to obtain an N-Boc-oxazolidinone as a colorless oil (1.48g). This product was dissolved in methanol (20mL), followed by addition of cesium carbonate (410mg) and stirring overnight at room temperature. Subsequently, the solvent was removed by distillation and the residue was dissolved in ethyl acetate. The mixture was then washed sequentially with diluted hydrochloric acid and water and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel chlomatography (hexane : ethyl acetate = 2 : 1) to give the desired product as a colorless oil (1.28g).

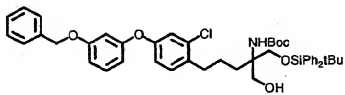
FABMS: 588 ([M+H]$^+$).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.51-1.66(3H, m), 1.82-1.85 (1H, m), 2.15(3H, s), 2.69(2H, t, J=7.3Hz), 2.75 (1H, d, J=13.4Hz), 2.90 (1H, d, J=13.4Hz), 3.69-3.70(2H, m), 4.02 (1H, br), 4.99 (1H, br s), 5.02 (2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.21-7.41(7H, m).

<Example 191>

5- [4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2- t-butoxycarbonylamino-2-t-butyldiphenylsiloxymethylpentane-1-ol

[0189]



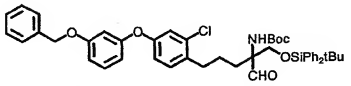
[0190] The compound of Example 146 (3.25g) was dissolved in DMF (18mL). To this solution, diisopropylethylamine (10.5mL) and t-$BuPh_2SiCl$ (1.73g) were added and the mixture was stirred for 8 hours at room temperature. Subsequently, ice water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water, diluted hydrochloric acid, water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane: ethyl acetate = 7 : 1) to give the desired product as a colorless oil (1.64g).

^{1}H-NMR(400MHz, $CDCl_3$)δ 1.06 (9H, s), 1.43 (9H, s). 1.49-1.82(4H, m), 2.66(2H, t, J=7.8Hz), 3.54 (1H, d, J=10.3Hz), 3.65-3.67(2H. m), 3.74(1H, d, J=10.3Hz) 5.03(2H. s). 5.05(1H. br s), 6.59(1H, dd, J=8.3, 2.4Hz), 6.63(1H, t, J=2.4Hz), 6.74(1H, dd. J=8.3, 2.4Hz), 6.82(1H, dd, J=8.3, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.10(1H, d, J=8.3Hz), 7.23(1H, t, J=8 3Hz). 7.31-7.45(11H, m), 7.61-7.64(4H, m).

<Example 192>

5- [4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2- t-butoxycarbonylamino-2-t-butyldiphenylsiloxymethylpentanal

[0191]



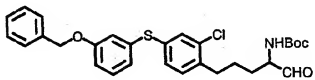
[0192] The compound of Example 191 (940mg) was dissolved in DMF (10mL). To this solution, pyridinium dichromate (800mg) was added and the mixture was stirred for 48 hours at room temperature. Following addition of water, the mixture was extracted with ethyl acetate. The extract was then washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous sodium sulfate. The solvent was concentrated and the residue was purified on a silica gel chlomatography (hexane : ethyl acetate = 3 : 1) to give the desired product as a coloriess oil (710mg).

^{1}H-NMR(400MHz, $CDCl_3$)δ 1.01(9H, s), 1.44(9H, s), 1.49-1.73(4H, m), 2.64(2H, br s), 3.84 (1H, d, J=10.3Hz), 4.13 (1H, d, J=10.3Hz), 5.03(2H, s), 5.43(1H, br s), 6.58(1H, dd, J=8.3, 2.4Hz), 6.62 (1H, t, J=2.4Hz), 6.74 (1H, dd, J=8.3, 2.4Hz) 6.82 (1H, dd, J=8.3, 2.4Hz), 6.99 (1H, d, J=2.4Hz), 7.08 (1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.30-7.43(11H, m), 7.56-7.64(4H, m), 9.36 (1H, s).

<Example 193>

5- [4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylaminopentanal

[0193]



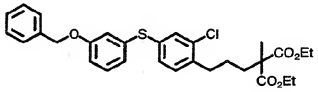
[0194] To an oxalyl chloride solution (1.0mL) of methylene chloride (20mL), a mixture of DMSO (1.7mL) and methylene chloride (10mL) was added while the mixtures were kept at - 78°C. The compound of Example 129 (5.59g) in methylene chloride (20mL) was then added dropwise. After 15min, triethylamine (7.2mL) was added and the mixture was stirred for 2 hours until room temperature. Following addition of water, the mixture was extracted with ethyl acetate and the organic phase was dried over anhydrous sodium sulfate. The solvent was then concentrated and the residue was purified on a silica gel chlomatography (hexane : ethyl acetate = 3 : 1) to give the desired product as a pale yellow oil (4.75g).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.60-1.74(3H, m), 1.96 (1H, br), 2.72-2.77(2H, m), 4.28 (1H, br), 5.02(2H, s), 6.87-6.95(3H, m), 7.10-7.16(2H, m), 7.23(1H, t, J=7.8Hz), 7.28-7.52(5H, m), 9.58 (1H, s).

<Example 194>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylpentanoate

[0195]

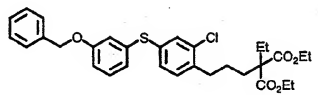


[0196] Sodium hydride (242mg) was dissolved in DMF (5mL). To this solution, diethyl methylmalonate (0.956mL) was added and the mixture was stirred for 30min. The compound of Reference Example 252 (2.50g) in DMF (5mL) was then added and the mixture was further stirred for 1 hour. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and was dried over anhydrous sodium sulfate. The dried organic phase was concentrated and the resulting residue was purified on a silica gel chlomatography (hexane: ethyl acetate = 20 : 1 to 10 : 1) to give the desired product as a yellow oil (2.74g).
MS (EI) : 540 ([M]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.23 (6H, t, J=7.3Hz), 1.40(3H, s), 1.52-1 60(2H, m), 1.91-1.95(2H, m), 2.70(2H, t, J=7.9Hz), 4.16(4H, q, J=7.3Hz), 5.02(2H, s), 6. 86-6. 94 (3H, m), 7.11-7.14(2H, m). 7.20-7.24(1H, m), 7.31-7.40(6H, m).

<Example 195>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylpentanoate

[0197]

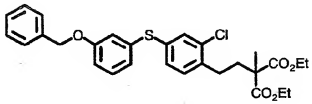


[0198] Using diethyl ethylmalonate, the reaction was carried out in the same manner as in Reference Example 194 to give the desired product as a yellow oil. MS (EI) : 554 ([M]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.80(3H, t, J=7.3Hz), 1.22(6H, t, J=7.3Hz), 1.45-1.53(2H, m), 1.89-1.97(4H, m), 2.70(2H, t, J=7.3Hz), 4.16(4H, q, J=7.3Hz), 5.02(2H, s), 6.86-6.94(3H, m). 7.11-7.16(2H, m), 7.20-7.24(1H, m), 7.31-7 40(6H, m).

<Example 196>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylbutyrate

[0199]

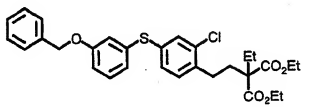


[0200] Using the compound of Reference Example 317, the reaction was carried out in the same manner as in Example 194 to give the desired product as a pale yellow oil. MS (EI) : 526 ([M]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.27(6H, t, J=7.3Hz), 1.52(3H, s), 2.10-2.14(2H, m), 2.65-2.69(2H, m), 4.20(4H, q, J=7.3Hz), 5.02(2H, s), 6.86-6.96(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.0), 7.31-7.41(6H, m).

<Example 197>

Ethyl 4- [4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylbutyrate

[0201]

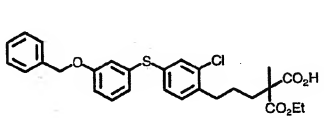


[0202] Using the compound of Reference Example 317, the reaction was carried out in the same manner as in Example 195 to give the desired product as a colorless oil.
MS (EI) : 540 ([M]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.82(3H, t, J=7.3Hz), 1.17 (6H, t, J=7.3Hz), 1.93 (2H, q, J=7.3Hz), 1.98-2.02(2H, m), 2.45-2.51(2H, m), 4.13(4H, q, J=7.3Hz), 5.10(2H, s), 6.92-7.01(3H, m), 7.21(1H, dd, J=8.0, 1.9Hz), 7.30-7.41(8H, m).

<Example 198>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylpentanoic acid

[0203]



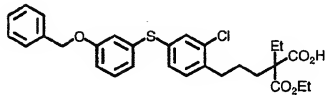
[0204] The compound of Example 194 (2.74g) was dissolved in ethanol (10mL). To this solution, potassium hydroxide (330mg) was added and the mixture was stirred overnight at 50°C. Subsequently, the reaction mixture was diluted with

water, followed by addition of 2mol/L hydrochloric acid and extraction with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride, was dried over anhydrous magnesium sulfate, and was then concentrated. The resulting residue was purified on a silica gel chromatography (hexane : ethyl acetate = 10 : 1 to 2 : 1) to give the desired product as a yellow oil (2.38g).
MS (EI) : 512 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.26(3H, t, J=7.3Hz), 1.47(3H, s), 1.53-1.62(2H, m), 1.92-2.03(2H, m), 2.71(2H, t, J=7.9Hz), 4.22(2H, q, J=7.3Hz), 5.02(2H, s), 6.87-6.94(3H, m), 7.10-7.14(2H, m), 7.21-7.25(1H, m), 7.31-7.40(6H, m).

<Example 199>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylpentanoic acid

[0205]

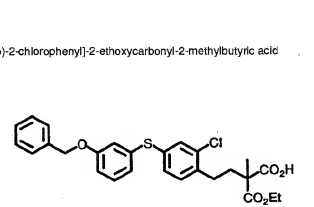


[0206] Using the compound of Example 195, the reaction was carried out in the same manner as in Example 198 to give the desired product as a yellow oil.
MS(EI): 526 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.84(3H, t, J=7.3Hz), 1.28(3H, t, J=7.3Hz), 1.42-1.59(2H, m), 1.85-1.95(2H, m), 2.00-2.13 (2H, m), 2.66-2.70(2H, m), 4.23-4.31(2H, m), 5.02(2H, s), 6.86-6.94(3H, m), 7.08-7.15(2H, m), 7.21-7.25(1H, m), 7.30-7.40(6H, m).

<Example 200>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-methylbutyric acid

[0207]

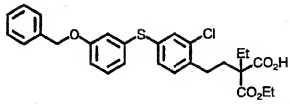


[0208] Using the compound of Example 196, the reaction was carried out in the same manner as in Example 198 to give the desired product as a pale yellow oil.
MS (EI) : 499 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.30(3H, t, J=7.3Hz), 1.57(3H, s), 2.11-2.19(2H, m), 2.69(2H, t, J=8.5Hz), 4.24(2H, q, J=7.3Hz), 5.02(2H, s), 6.87-6.96(3H, m), 7.14(2H, s), 7.23 (1H, t, J=8.0Hz), 7.31-7.40(6H, m).

<Example 201>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-ethylbutyric acid

[0209]

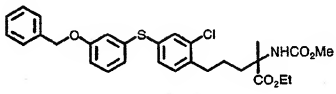


[0210] Using the compound of Example 197, the reaction was carried out in the same manner as in Example 198 to give the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.90(3H, t, J=7.3Hz), 1.33(3H, t, J=7.3Hz), 1.94-1.99(1H, m), 2.05-2.12(1H, m), 2.19-2.24 (2H, m), 2.59-2.64(2H, m), 4.20-4.31(2H, m), 5.02(2H, s), 6.87-6.94(3H, m), 7.09-7.14(2H, m), 7.23(1H, t, J=8.0Hz), 7.29-7.40(6H, m).

<Example 202>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentanoate

[0211]

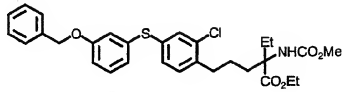


[0212] The compound of Example 198 (2.38g) was dissolved in benzene (20mL). To this solution, triethylamine (0.711mL) and DPPA (1.10mL) were added. The mixture was then stirred for 10min at room temperature and for a further 1 hour and 30min while being refluxed. Subsequently, methanol (3.76mL) was added over 30min and the mixture was stirred overnight. The reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of sodium chloride and was dried over anhydrous magnesium sulfate. The dried organic phase was concentrated and the resulting residue was purified on a silica gel chromatography (hexane: ethyl acetate = 20 : 1 to 10 : 1) to give the desired product as a yellow oil (2.04g).
MS (EI) : 541 ([M]$^+$) .
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(3H, t, J=7.3Hz), 1.36-1.40 (1H, m), 1.54(3H, s), 1.56-1.65(1H, m), 1.80-1.87(1H, m), 2.28(1H, m), 2.65-2.69(2H, m), 3.63(3H, s), 4.15-4.22(2H, m), 5.02(2H, s), 5.61(1H, br s), 6.86-6.94(3H, m), 7.09-7.15 (2H, m), 7.20-7.24(1H, m), 7.31-7.40(6H, m).

<Example 203>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentanoate

[0213]

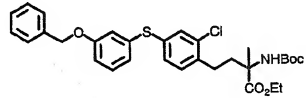


[0214] Using the compound of Example 199, the reaction was carried out in the same manner as in Example 202 to obtain the desired product as a yellow oil.
MS (EI) : 555 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.74(3H, t, J=7.3Hz), 1.24(3H, t, J=7.3Hz), 1.28-1.32(1H, m), 1.57-1.58(1H, m), 1.70-1.84 (2H, m), 2.34-2.44(2H, m), 2.62-2.72(2H, m), 3.63(3H, s), 4.16-4.22(2H, m), 5.02(2H, s), 5.78(1H, br s), 6.86-6.94(3H, m), 7.08-7.15(2H, m), 7.20-7.24(1H, m), 7.31-7.40(6H, m).

<Example 204>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutyrate

[0215]

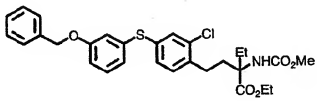


[0216] Using the compound of Example 200 and t-butanol instead of methanol, the reaction was carried out in the same manner as in Example 202 to obtain the desired product as a pale yellow oil.
FABMS: 569([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.29(3H, t, J=7.3Hz), 1.46(9H, s), 1.58(3H, s), 2.10(1H, td, J=13.0, 4.9Hz), 2.41(1H, br), 2.53(1H, td, J=13.0, 4.9Hz), 2.67(1H, td, J=13.0, 4.9Hz), 4.19(2H, q, J=7.3Hz), 5.02(2H, s), 5.46 (1H, br s), 6.86-6.94 (3H m), 7.08-7.15(2H, m), 7.23(1H, t, J=8.0Hz), 7.30-7.40(6H, m).

<Example 205>

Ethyl 4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminobutyrate

[0217]



[0218] Using the compound of Example 201, the reaction was carried out in the same manner as in Example 202 to obtain the desired product as a pale yellow oil

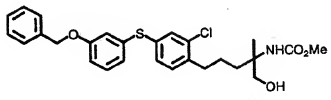
MS (EI) : 541 ([M]+).

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.77(3H, t, J=7.3Hz), 1.30(3H, t, J=7.3Hz), 1.75-1.80(1H, m), 2.05-2.15(1H, m), 2.36-2.49 (2H, m), 2.59-2.68(2H, m), 3.66(3H, s), 4.11-4.27(2H, m), 5.02(2H, s), 5.87(1H, br), 6.86-6.93(3H, m), 7.08-7.14(2H, m), 7.22(1H, t, J=8.0Hz), 7.30-7.40(6H, m).

<Example 206>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentane-1-ol

[0219]



[0220] Using the compound of Example 202, the reaction was carried out in the same manner as in Example 76 to obtain the desired product as a colorless oil.

MS (EI) : 499 ([M]+).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.18(3H, s), 1.57-1.84 (4H, m), 2.71(2H, t, J=7.3Hz), 3.59-3.69(3H, m), 3.63(3H, s), 4.71 (1H, br s), 5.02(2H. s), 6.86-6.94(3H, m), 7.13-7.17(2H, m), 7.21-7.25(1H, m), 7.30-7.41(6H, m).

<Examples 207 and 208>

(+) and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-methylpentane-1-ols

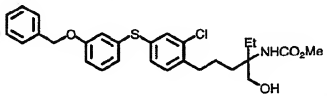
[0221] The compound of Example 206 was optically resolved by a high performance liquid chromatography (HPLC) (chiralcel OD. hexane : isopropanol = 70 : 30, detection wavelength = UV 254nm, flow rate = 3mL/min).

[0222] The compound obtained from the first eluate had an optical rotation $[\alpha]^{24}{}_D$ of +15 ° (C = 1.0, chloroform) (Example 207), while the compound obtained from the second eluate had an optical rotation $[\alpha]^{24.7}{}_D$ of -12° (C = 1.0, chloroform) (Example 208).

<Example 209>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentane-1-ol

[0223]



[0224] Using the compound of Example 203, the reaction was carried out in the same manner as in Example 76 to obtain the desired compound as a pale yellow oil.
MS (EI) : 513 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.83(3H, t, J=7.3Hz), 1.51-1.73(6H, m), 2.70 (2H, t, J=7.3Hz), 3.63(3H, s), 3.65-3.70(3H, m), 4.63(1H, br s), 5.02(2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.20-7.24 (1H, m), 7.30-7.40 (6H, m).

<Examples 210 and 211>

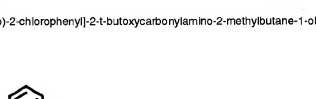
(+) and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminopentane-1-ols

[0225] The compound of Example 209 was optically resolved by HPLC (chiralcel OD, hexane : isopropanol = 60 : 40, detection wavelength = UV 254nm, flow rate = 3mL/min).
[0226] The colorless oil obtained from the first eluate had an optical rotation $[\alpha]^{25.6}_D$ of +14° (C = 1.0, chloroform) (Example 210), while the colorless oil obtained from the second eluate had an optical rotation $[\alpha]^{25.7}_D$ of -15° (C = 1.0, chloroform) (Example 211).

<Example 212>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutane-1-ol

[0227]



[0228] Using the compound of Example 204, the reaction was carried out in the same manner as in Example 76 to obtain the desired compound as a colorless oil.
MS (EI) : 527 ([M]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.25(3H, s), 1.44 (9H, s), 1.82 (1H, td, J=13.0, 4.9Hz), 2.06(1H, td, J=13.0, 4.9Hz), 2.65-2.80(2H, m), 3.68-3.74(2H, m), 4.68 (1H, br s), 5.02 (2H, s), 6.86-6.94(3H, m), 7.15(2H, s), 7.23(1H, t, J=8.0Hz), 7.32-7.40(6H, m).

<Examples 213 and 214>

(+) and (-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methylbutane-1-ols

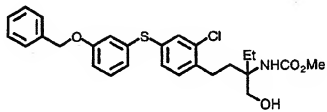
[0229] The compound of Example 212 was optically resolved by HPLC (chiralpak AD, hexane : isopropanol = 85 : 15, detection wavelength = UV 254nm, flow rate = 3mL/min).

[0230] The colorless oil obtained from the first eluate had an optical rotation $[\alpha]^{25.3}_{D}$ of +4.6° (C = 1.0, chloroform) (Example 213), while the colorless oil obtained from the second eluate had an optical rotation $[\alpha]^{25.6}_{D}$ of -2.2 °(C = 1.0, chloroform) (Example 214).

<Example 215>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminobutane-1-ol

[0231]



[0232] Using the compound of Example 205, the reaction was carried out in the same manner as in Example 76 to obtain the desired product as a colorless oil.

MS (EI) : 499 ([M]+).

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.94(3H, t, J=7.3Hz), 1.69(2H, q, J=7.3Hz), 1.80-1.94(2H, m), 2.62-2.75(2H, m), 3.65(3H, s), 3.77(3H, m), 4.77(1H, br), 5.02(2H, s), 6.86-6.95(3H, m), 7.16(2H, s), 7.23(1H, t, J=8.0Hz), 7.32-7.41(6H, m).

<Examples 216 and 217>

(+) and (-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-2-methoxycarbonylaminobutane-1-ols

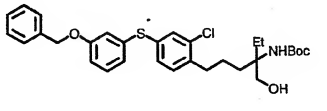
[0233] The compound of Example 215 was optically resolved under similar conditions to those used in Examples 213 and 214.

[0234] The colorless oil obtained from the first eluate had an optical rotation $[\alpha]^{25.6}_{D}$ of +11.1° (C = 1.0, chloroform) (Example 216), while the colorless oil obtained from the second eluate had an optical rotation $[\alpha]^{26.1}_{D}$ of -9.67° (C = 1.0, chloroform) (Example 217).

<Example 218>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-butoxycarbonylamino-2-ethylpentane-1-ol

[0235]

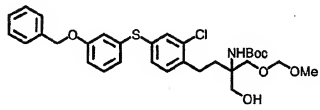


[0236] Using the compound of Example 199 and t-butanol instead of methanol, the same procedure was followed as in Example 203 and the reactant was reduced in the same manner as in Example 76 to obtain the desired product as a colorless oil.
MS (EI): 555 ([M]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 0.83(3H, t, J=7.3Hz), 1.42(9H, s) : 1.55-1.72(6H, m), 2.70(2H, t, J=6.7Hz), 3.64-3.66(2H, m), 4.49(1H, br s), 5.02(2H, s), 6.82-6.95(3H, m), 7.12-7.17(2H, m), 7.20-7.25(1H, m), 7.30-7.41(6H, m).

<Example 219>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethylbutnane-1-ol

[0237]



[0238] The compound of Example 126 (4.00g) was dissolved in methylene chloride (100mL). To this solution, diisopropylethylamine (1.54mL) was added, followed by dropwise addition of methoxymethylchloride (710mg) at 0°C. The mixture was stirred for one day until room temperature. Following addition of ice water, the mixture was extracted with ethyl acetate. The extract was then dried over anhydrous sodium sulfate and the solvent was removed by distillation. The resulting residue was purified on a silica gel chlomatography (hexane : ethyl acetate = 2 : 1) to give the desired product as a colorless oil (2.60g).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.90-2.00(2H, m), 2.68-2.78(2H, m), 3.39(3H, s), 3.54 (1H d, J=9.8Hz), 3.77 (2H, d, J=6.1Hz), 3.79(1H, d, J=9.8Hz), 3.99(1H, br), 4.65(2H, s), 5.02(2H, s), 5.20(1H, br s), 6.86-6.94(3H, m), 7.13-7.17(2H, m), 7.22(1H, t, J=8.0Hz), 7.31-7.40(6H, m).

<Examples 220 and 221>

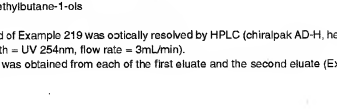
(+) and (-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethylbutane-1-ols

[0239] The compound of Example 219 was optically resolved by HPLC (chiralpak AD-H, hexane : isopropanol = 85 : 15, detection wavelength = UV 254nm, flow rate = 3mL/min).
[0240] A colorless oil was obtained from each of the first eluate and the second eluate (Example 220 and Example 221, respectively).

<Example 222>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-butoxycarbonylamino-2-methoxymethyloxymethylpentane-1-ol

[0241]

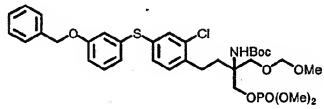


[0242] Using the compound of Example 128, the reaction was carried out in the same manner as in Example 219 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.56-1.68(3H, m), 1.81-1.84(1H, m), 2.67(2H, t, J=7.8Hz), 3.35(3H, s), 3.46 (1H, d, J=9.8Hz), 3.66-3.68(2H, m), 3.71(1H, d, J=9.8Hz), 4.61(2H, s), 5.02(2H, s), 5.07(1H, br s), 6.87(1H, ddd, J=8.3, 2.5, 1.0Hz), 6.91-6.95(2H, m), 7.12-7.16(2H, m), 7.23(1H, t, J=7.8Hz), 7.31-7.40(6H, m).

<Example 223>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethyl-1-dimethoxyphosphoryloxybutane

[0243]



[0244] To a methylene chloride solution (2mL) containing the compound of Example 219 (660mg), carbon tetrabromide (533mg) and pyridine (2mL), trimethyl phosphite (0.19mL) was added while the mixture was stirred at 0°C and the mixture was stirred for 5 hours until room temperature. Subsequently, water was added and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to obtain the desired product as a colorless oil (830mg).
FABMS: 696 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.95-2.03(1H, m), 2.08-2.21(1H, m), 2.69-2.78(2H, m), 3.39(3H, s), 3.68(1H, d, J=9.8Hz), 3.74(1H, d, J=9.8Hz), 3.78(6H, d, J=11.0Hz),4.22-4.29(2H, m), 4.65(2H, s), 4.97(1H, br s), 5.02(2H, s), 6.88 (1H, dd, J=7.9, 2.4Hz), 6.91-6.95(2H, m), 7.14(2H, s), 7.23(1H, t, J=7.8Hz), 7.31-7.40(6H, m).

<Example 224>

(-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl] -2-t-butoxycarbonylamino-2-methoxymethyloxymethyl-1-dimethoxyphosphoryloxybutane

[0245] Using the compound of Example 220 (first eluate), the reaction was carried out in the same manner as in Example 223 to obtain the desired product as a colorless oil. $[\alpha]^{26}_D$ = -3.01°(C = 0.93, chloroform).

<Example 225>

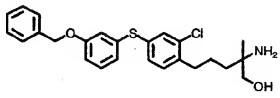
(+)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethyl-1-dimethoxyphosphoryloxybutane

[0246] Using the compound of Example 221 (second eluate), the reaction was carried out in the same manner as in Example 223 to obtain the desired product as a colorless oil.
$[\alpha]^{28}_D$ = +1.39°(C = 1.03, chloroform).

<Example 226>

(±)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol

[0247]



[0248] The compound of Example 206 (527mg) was dissolved in a mixed solvent composed of a 5mol/L aqueous solution of potassium hydroxide (2mL), tetrahydrofuran (2mL) and methanol (3mL). This mixture was refluxed and stirred for 4 days. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The ethyl acetate layer was then washed with a saturated aqueous solution of sodium chloride, was dried over anhydrous magnesium sulfate, and was then concentrated. The resulting residue was purified on a silica gel column chromatography (aminated silica gel, ethyl acetate : ethanol = 20 : 1) to give the desired product as a pale yellow oil (311mg).
FABMS: 442 ([M+H]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.04(3H, s), 1.37-1.67(4H, m), 2.70 (2H, t, J=7.3Hz), 3.29 (2H, q, J=9.2Hz), 5.02(2H, s), 6.86-6.94(3H, m), 7.12-7.17(2H, m), 7.21-7.25(1H, m), 7.31-7.41(6H, m).

<Example 227>

(+)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol

[0249] Using the compound of Example 207 (first eluate), the reaction was carried out in the same manner as in Example 226 to obtain the desired product as a pale yellow oil.

Elemental analysis (%) : $C_{25}H_{28}ClNO_2S \cdot 1/3H_2O$			
	C	H	N
Calcd	67.00	6.45	3.13
Found	67.03	6.51	3.20

$[\alpha]^{25.2}_D$ +2.0° (C = 1.0, chloroform)

<Example 228>

(-)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentane-1-ol

[0250] Using the compound of Example 208 (second eluate), the reaction was carried out in the same manner as in Example 226 to give the desired product as a pale yellow oil.

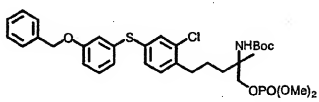
Elemental analysis (%) : $C_{25}H_{28}ClNO_2S \cdot 1/4H_2O$			
	C	H	N
Calcd	67.23	6.44	3.14
Found	67.19	6.44	3.15

$[\alpha]^{25.5}_D$ -2.6° (C = 1.0, chloroform)

<Example 229>

(+)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-1-dimethoxyphosphoryloxy-2-methylpentane

[0251]



[0252] The compound of Example 227 (410mg) was dissolved in acetonitrile (10mL). While this solution was chilled in an ice bath, Boc_2O (303mg) was added and the mixture was stirred for 3 hours at room temperature. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. This solution was washed with water and a saturated aqueous solution of sodium chloride. The organic phase was then dried over anhydrous sodium sulfate and was concentrated. The resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give a t-butoxycarbonylamino product as a pale yellow oil (473mg). The resulting compound (473mg), along with carbon tetrabromide (434mg), was dissolved in pyridine (2.00mL). While this solution was chilled in an ice bath, trimethyl phosphite (0.205mL) was added and the mixture was allowed to warm to room temperature and was stirred for 2 hours. Subsequently, the reaction mixture was diluted with water and was extracted with ethyl acetate. The extract was then washed with a saturated aqueous solution of sodium chloride, was dried over anhydrous magnesium sulfate, and was then concentrated. The resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 5 : 1 to 1 : 1) to give the desired product as a pale yellow oil (534mg).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.25(3H, s), 1.41(9H, s), 1.58-1.91(4H, m), 2.70(2H, t, J = 7.3Hz), 3.77(6H, d, J=11.0Hz), 3.96-4.00(1H, m), 4.13-4.16(1H, m), 4.51(1H, brs), 5.02(2H, s), 6.86-6.89(1H, m), 6.92-6.96(2H, m), 7.11-7.16(2H, m), 7.23(1H, t, J = 7.9Hz), 7.31-7.34(2H, m), 7.35-7.39(4H, m).

<Example 230>

(-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-1-dimethoxyphosphoryloxy-2-methylpentane

[0253] Using the compound of Example 228, the reaction was carried out in the same manner as in Example 229 to obtain the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.25(3H, s), 1.41(9H, s), 1.58-1.91(4H, m), 2.70(2H, t, J = 7.3Hz), 3.77(6H, d, J=11.0Hz), 3.97-4.00(1H, m), 4.13-4.17(1H, m), 4.51(1H, brs), 5.02(2H, s), 6.86-6.89(1H, m), 6.92-6.95(2H, m), 7.11-7.16(2H, m), 7.23(1H, t, J = 7.9Hz), 7.32-7.34(2H, m), 7.35-7.40(4H, m).

<Example 231>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-methoxymethyloxymethyl-1-dimethoxyphosphoryloxypentane

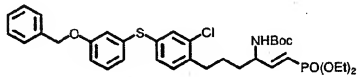
[0254]

[0255] Using the compound of Example 222, the reaction was carried out in the same manner as in Example 223 to obtain the desired product as a colorless oil.
FABMS: 710 ([M+H]+).
^{1}H-NMR(400OMHz, $CDCl_3$) δ 1.41(9H, s), 1.57-1.62(2H, m), 1.76-1.80(1H, m), 2.00-2.05(1H, m), 2.70(2H, t, J=7.8Hz), 3.34(3H, s), 3.57(1H, d, J=9.5Hz), 3.65(1H, d, J=9.5Hz), 3.77(6H, d, J=11.0Hz), 4. 12 (2H, d, J=7.1Hz), 4.60(2H, s), 4.81(1H, br s), 5.02(2H, s), 6.87(1H ddd, J=8.3, 2.5, 1.0Hz), 6.92-7.00(2H, m), 7.10-7.16(2H, m), 7.23(1H, t, J=7.8Hz), 7.28-7.52(6H, m).

<Example 232>

Diethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-1-hexenylphosphonate

[0256]

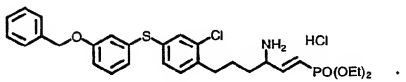


[0257] Ethyl methylenebisphosphonate (940mg) in THF (5mL) was chilled to -78°C under an argon gas atmosphere. To this solution, a 1.6mol/L n-BuL-hexane solution (2mL) was added dropwise and the mixture was stirred for 30min, followed by dropwise addition of a THF solution (15mL) of the compound of Example 193 (1.58g). After 3 hours, a saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous solution of sodium chloride and was dried over anhydrous sodium sulfate. The solvent was removed by distillation to give the desired product as a colorless oil (1.71g).
FABMS: 660([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.29-1.33(6H, m). 1.43(9H, s), 1.54-1.68(4H, m), 2.71-2.73(2H, m), 4.03-4.11 (4H, m), 4.32 (1H, br), 4 47 (1H, br), 5.03(2H, s), 5.77 (1H, t, J=17.7Hz), 6.60-6.71 (1H, m), 6.87-6.98(3H, m), 7.09-7.15(2H, m), 7.21-7.41(7H, m).

<Example 233>

Diethyl 3-amino-6- [4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1-hexenylphosphonate hydrochloride

[0258]

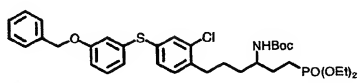


[0259] The compound of Example 232 (300mg) was dissolved in methanol (10mL) containing 10% hydrochloric acid in an ice bath. The mixture was stirred for 6 hours until room temperature and the solvent was concentrated. This gave the desired product as a colorless oil (250mg).
FABMS: 560 ([M+H]+).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.16-1.22(6H, m), 1.53-1.77(4H, m), 2.68-2.69(2H, m), 3.05(1H, br), 3.94-4.07(4H, m), 5.09(2H, s). 6.13(1H, t, J=17.6Hz). 6.46-6.55(1H, m), 6.89-7.00(3H, m), 7.20-7.22(1H, m), 7.29-7.41(8H, m), 8.44(3H. br s).

<Example 234>

Diethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylaminohexylphosphonate

[0260]

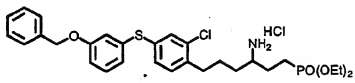


[0261] The compound of Example 232 was reduced in the same manner as in Reference Example 125 to obtain the desired product as a colorless oil.
FABMS: 662([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.32(6H, t, J=7.3Hz), 1.43 (9H, s), 1.46-1.82(8H, m), 2.67-2.73(2H, m), 3.62(1H, br), 4.03-4.13(4H, m), 4.32-4.34(1H, br), 5.02(2H, s), 6.86-6.95(3H, m), 7.10-7.16(2H, m), 7.23(1H, t, J=8.0Hz), 7.32-7.40 (6H, m).

<Example 235>

Diethyl 3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]hexylphosphonate hydrochloride

[0262]

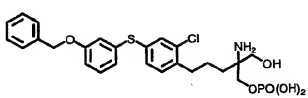


[0263] The compound of Example 234 was reacted in the same manner as in Example 233 to obtain the desired product as a pale brown oil.
FABMS: 562 ([M+H]+).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.21(6H, t, J=6.7Hz), 1.59-1.85(8H, m), 2.67(2H, br s). 3.15(1H, br s), 3.91-4.01(4H, m), 5.08(2H, s), 6.88-6.99(3H, m), 7.21-7.39(9H, m), 8.08(3H, br s).

<Example 236>

2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylpentylphosphonate monoester

[0264]



[0265] To an acetonitrile solution (5mL) of the compound of Example 231 (500mg), TMSI (0.5mL) was added and

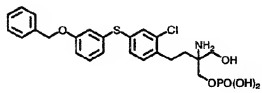
the mixture was stirred for 3 hours. The solvent was concentrated and the residue was purified on a silica gel column chromatography to obtain the desired product as a colorless powder (120mg).
FABMS: 538 ([M+H]⁺).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.60(4H, br s), 2.63(2H, br s), 3.38-3.44(2H, m), 3.72(2H, br s), 5.08(2H, s), 6.87-6.98 (3H, m), 7.20-7.38(9H, m).

Elemental analysis (%): $C_{25}H_{29}ClNO_6SP \cdot H_2O$			
	C	H	N
Calcd	54.00	5.62	2.52
Found	54.10	5.37	2.62

<Example 237>

2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonate monoester

[0266]



[0267] Using the compound of Example 223, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 524 ([M+H]⁺).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.77-1.78 (2H, m), 2.71-2.75 (2H, m), 3.50-3.58(2H, m), 3.76-3.88(2H, m), 5.08(2H, s), 6.89(1H, t, J=7.3Hz), 6.96-6.99(2H, m), 7.21-7.38(9H, m).

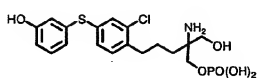
Elemental analysis (%) : $C_{24}H_{27}ClNO_6SP$			
	C	H	N
Calcd	55.01	5.19	2.67
Found	54.94	5.26	2.77

m.p. = 200-202°C

<Example 238>

2-amino-5-[2-chloro-4-(3-hydroxyphenylthio)phenyl]-2-hydroxymethylpentylphosphonate monoester

[0268]



[0269] Instead of ice-cold environment, the experiment of Example 236 was carried out at room temperature to give the desired product as a colorless powder.

FABMS: 448 ([M+H]$^+$).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.54-1.62(4H, m), 2.51-2.73 (2H, m), 3.37-3.41(2H, m), 3.57-3.75(2H, m), 6.62(1H, dd, J=8.0, 1.8Hz), 6.67-6.68 (1H, m), 6.75 (1H, dd, J=8.6, 1.2Hz), 7.15 (1H, t, J=8.0Hz), 7.27 (1H, dd, J=8.0, 2.0Hz), 7.34-7.36(2H, m).

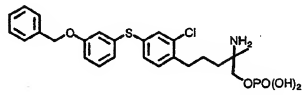
Elemental analysis(%) : $C_{16}H_{23}ClNO_6SP{\cdot}0.5H_2O$			
	C	H	N
Calcd	47.32	5.29	3.07
Found	47.06	5.07	3.07

m.p. = 180-182°C.

<Example 239>

(+)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentylphosphonate monoester

[0270]



[0271] The compound of Example 229 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder.
HR-MS(FAB+): 522.1255 (-1.6mmu).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.12(3H, s), 1.51-1.65(4H, m), 2.64-2.70(2H, m), 3.66(2H, d, J = 11Hz), 5.09(2H, s), 6.91(1H, d, J = 7.3Hz), 6.97-7.01(2H, m), 7.20-7.24(1H, m), 7.30-7.42(8H, m).

Elemental analysis(%) : $C_{25}H_{29}ClNO_5PS{\cdot}1/2H_2O$			
	C	H	N
Calcd	56.55	5.69	2.64
Found	56.40	5.60	2.77

$[\alpha]^{22.6}_D$ +3.2° (C = 1.0, methanol).
m.p. = 207-210°C.

<Example 240>

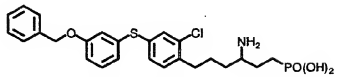
(-)-2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentylphosphonate monoester

[0272] Using the compound of Example 228, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
HR-MS(FAB+): 522.1277 (+0.6mmu).
^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.12(3H, s), 1.51-1. 65 (4H, m), 2.63-2.70(2H, m), 3.67(2H, d, J = 12Hz), 5.09(2H, s), 6. 89-6. 92 (1H, m), 6.96-7.01(2H, m), 7.22-7.24(1H, m), 7.32-7.42(8H, m).
$[\alpha]^{23.4}_D$ -3.1° (C = 1.0, methanol).
m.p. = 200-203°C.

<Example 241>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]hexylphosphonic acid

[0273]



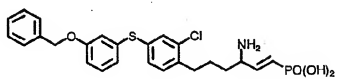
[0274] Using the compound of Example 234, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 506([M+H]$^+$).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.56-1.72(8H, m), 2.67(2H, br s), 3.18(1H, br s), 5.08(2H, s), 6.88-7.00(3H, m), 7.21-7.40 (9H, m).

Elemental analysis (%) : $C_{25}H_{29}ClNO_4PS \cdot 1/2H_2O$			
	C	H	N
Calcd	58.30	5.87	2.72
Found	58.29	5.71	2.80

<Example 242>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1-hexenylphosphonic acid

[0275]

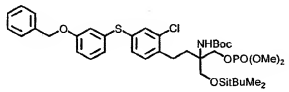


[0276] Using the compound of Example 232, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 504 ([M+H]$^+$)
^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.53-1.70(4H, m), 2.69(2H, t, J=7.3Hz), 3.83-3.99 (1H, m), 5.12(2H, s), 6.03 (1H, t, J=16.5Hz), 6.26 (1H, d,d,d, J=16.5, 10.0, 7.3Hz), 6.89-7.01(3H, m), 7.20-7.41(9H, m).

<Example 243>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-t-butyldimethylsiloxymethyl-1-dimethoxyphosphoryloxybutane

[0277]

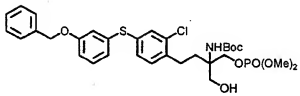


[0278] The compound of Example 126 was reacted with t-$BuMe_2SiCl$ in the same manner as in Example 191. The resulting compound was reacted in the same manner as in Example 223 to give the desired product as a colorless oil.
FABMS: 766([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.09(6H, s), 0.91(9H, s), 1.45(9H, s), 1.86-1.98(1H, m), 2.05-2.15(1H, m), 2.72(2H, t, J=8.6Hz), 3.72(2H, s), 3.78(6H, d, J=11.0Hz), 4.17-4.24(2H, m), 4.78(1H, br s), 5.02(2H, s), 6.86-6.95(3H, m), 7.21(2H,s), 7.23(1H, t, J=7.3Hz), 7.31-7.41(6H, m).

<Example 244>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-hydroxymethyl-1-dimethoxyphosphoryloxybutane

[0279]



[0280] To a THF solution (30mL) of the compound of Example 243 (2.70g), 1mol/L tetrabutylammonium fluoride in THF (5mL) was added and the mixture was stirred for 1 hour at room temperature. Following addition of water, the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to obtain the desired product as a colorless oil (2.30g).
FABMS: 652 ([M+H]+)
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.83-1.90(1H, m), 2.09-2.17(1H, m), 2.71(2H, t, J=8.6Hz), 3.71-3.77(2H, m), 3.79(6H, d, J=11.0Hz), 4.04(1H, br), 4.17-4.29(2H, m), 5.00(1H, br s), 5.02(2H, s), 6.86-6.95(3H, m), 7.14-7.15(2H, m), 7.23(1H, t, J=7.3Hz), 7.31-7.39(6H, m).

<Examples 245 and 246>

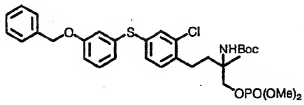
(+) and (-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-t-butyldimethylsiloxymethyl-1-dimethoxyphosphoryloxybutanes

[0281] The compound of Example 244 was optically resolved by HPLC (chiralpak AS-H, hexane : isopropanol = 8 : 2, detection wavelength = UV 254nm, flow rate = 1mL/min). The colorless oil obtained from the first eluate had an optical rotation $[\alpha]^{26}_D$ of -6.12° (C = 1.0, methanol) (Example 245), while the colorless oil obtained from the second eluate had an optical rotation $[\alpha]^{27}_D$ of +5.79° (C = 1.0, methanol) (Example 246).

<Example 247>

(+)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-1-dimethoxyphosphoryloxy-2-methylbutane

[0282]



[0283] Using the compound of Example 213, the reaction was carried out in the same manner as in Example 223 to obtain the desired product as a pale brown oil.
FABMS: 636([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.36(3H, s), 1.44 (9H, s), 1.77-1.82 (1H, m), 2.05-2.15(1H, m), 2.68-2.74(2H, m), 3.78(6H, d, J=11.0Hz), 4.01-4.05(1H, m), 4.21-4.25 (1H, m), 4.63(1H, br), 5.02(2H, s), 6.87-6.94(3H, m), 7.23-7.27(3H, m), 7.32-7.42(6H, m).

<Example 248>

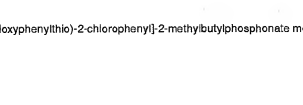
(-)-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-1-dimethoxyphosphoryloxy-2-methylbutane

[0284] Using the compound of Example 214, the reaction was carried out in the same manner as in Example 223 to obtain the desired product as a pale brown oil.
FABMS: 636 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.36(3H, s), 1.44(9H, s), 1.74-1.82(1H, m), 2.05-2.15(1H, m), 2.66-2.76(2H, m), 3.78(6H, d, J=11.0Hz), 4.01-4.05(1H, m), 4.21-4.25 (1H, m), 4.63(1H, br), 5.02(2H, s), 6.86-6.95(3H, m), 7.21-7.27(3H, m), 7.31-7.41(6H, m).

<Example 249>

(+)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutylphosphonate monoester

[0285]



[0286] Using the compound of Example 247, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 508([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSOd_6$-TFA) δ 1.29(3H, s), 1.72-1.84(2H, m), 2.71(2H, t, J=7.9Hz), 3.87(1H, dd, J=4.9, 11.0Hz),

3.93(1H dd, J=4.9, 11.0Hz), 5.08(2H, s), 6.91(1H, d, 7.3Hz), 6.96-7.01(2H, m) 7.23(1H, dd, J=1.8, 7.9Hz), 7.29-7.40 (8H, m).
$[\alpha]^{25.6}_{D}$ +15.1°(C = 1.0, 10%TFA in DMSO).

Elemental analysis (%) :$C_{24}H_{27}ClNO_5PS$·2/3 CF_3CO_2H			
	C	H	N
Calcd	52.10	4.78	2.40
Found	52.29	4.75	2.68

<Example 250>

(-)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutylphosphonate monoester

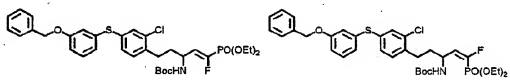
[0287] Using the compound of Example 248, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 508 ([M+H]+).
^{1}H-NMR (400MHz, DMSO-TFA) δ 1.29(3H, s), 1.76-1.90(2H, m), 2.71(2H, t, J=7.9Hz), 3.87 (1H, dd, J=4.9, 11.0Hz), 3.93(1H, dd, J=4.9, 11.0Hz), 5.08(2H, s), 6.90-7.01(3H, m), 7.24(1H, dd, J=1.8, 7.9Hz), 7.29-7.40(8H, m).
$[\alpha]^{26.3}_{D}$ -12.6°(C = 1.0, 10%TFA in DMSO).

Elemental analysis(%) : $C_{24}H_{27}ClNO_5PS$·1/2H_2O			
	C	H	N
Calcd	55.76	5.46	2.71
Found	55.77	5.19	2.97

<Examples 251 and 252>

Diethyl (Z)- and (E)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-1-fluoro-1-pentenylphosphonates

[0288]



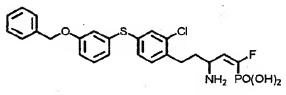
[0289] The compound of Example 127 was oxidized in the same manner as in Example 193 to obtain an aldehyde for use in the subsequent reaction.
[0290] Meanwhile, trimethylchlorosilane (1.0mL) was added to diethyl dibromofluoromethylphosphate (1.48mL) in THF (75mL), and the mixture was cooled to -78°C. Subsequently, 1.6mol/L n-butyllithium in hexane (11.3mL) was added dropwise and the mixture was stirred for 40min. Subsequently, the aldehyde obtained above (3.68g) in THF (25.0mL) was added dropwise over 10min. The mixture was allowed to warm to 0°C and was stirred for 5 hours. Following addition of aqueous ammonium chloride, the mixture was extracted with ethyl acetate. The ethyl acetate layer was then washed with a saturated aqueous solution of sodium chloride, was dried over anhydrous sodium sulfate, and was concentrated. The resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 10 : 1 to 1 : 1) As a result, the Z-form was obtained from the first eluate as a yellow oil (1.70g), and the E-form was obtained from the second eluate as a yellow oil (667mg).
Z-form : Example 251
FABMS: 664([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.31-1.38(6H, m), 1.43(9H, s), 1.88-2.00(2H, m), 2.69-2.83(2H, m), 4.13-4.22(4H, m), 4.80-4.90(1H, m), 5.02(2H, s), 5.15-5.30(1H, br), 6.08-6.30(1H, m), 6.87-6.88(1H, m), 6.90-6.95(2H, m), 7.11-7.15(2H,

m), 7.22(1H, t, J=7.9Hz), 7.31-7.39(6H, m).
E-form : Example 252
FABMS: 663 ([M]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.34-1.36(6H, m), 1.44(9H, s), 1.82-1.88(2H, m), 2.71-2.78(2H, m), 4.15-4.23(4H, m), 4.60-4.65(2H, m), 5.02(2H, s), 5.80-6.00(1H, m), 6.89 (1H, dd, J=1.4, 7.9Hz), 6.93-6.95 (2H, m), 7.11-7.17(2H, m), 7.23 (1H, t, J=7.9Hz), 7.31-7.41(6H, m).

<Example 253>

(Z)-3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1-fluoro-1-pentenylphosphonic acid

[0291]



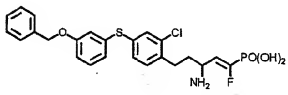
[0292] Using the compound of Example 251, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 508([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSd_6$) δ 1.78-1.98 (2H, m), 2.69(2H, t, J=7.9Hz), 4.19(1H, br), 5.08(2H, s), 5.47-5.62(1H, m), 6.90(1H, d, J=7.9Hz), 6.97-6.99(2H, m), 7.20(1H, d, J=7.9Hz), 7.29-7.40(8H, m), 8.67 (2H, br).
m.p. = 285-288°C.

Elemental analysis (%) :$C_{24}H_{24}ClFNO_4PS\cdot 13/10H_2O$			
	C	H	N
Calcd	54.25	5.05	2.64
Found	54.54	5.49	2.44

<Example 254>

(E)-3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1-fluoro-1-pentenylphosphonic acid

[0293]

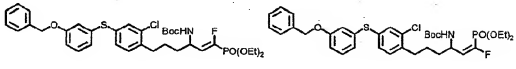


[0294] Using the compound of Example 252, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 508 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.79-1.91 (1H, m), 1.91-2.02(1H, m), 2.58-2.70(2H, m), 3.84-3.98(1H, m), 5.08(2H, s), 5.43-5.62(1H, m), 6.90(1H, m), 6.95-6.99(2H, m), 7.17-7.38(9H, m), 8.68(2H, br).
m.p. = 288-290°C.

<Examples 255 and 256>

Diethyl (Z)- and (E)-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-1-fluoro-1-hexenylphosphonates

[0295]



[0296] The compound of Example 193 was reacted in the same manner as in Examples 251 and 252 to obtain the desired Z-form (Example 255) and the E-form (Example 256), respectively. Each product was obtained as a yellow oil.

Z-form : Example 255

FABMS: 678 ([M+H]+).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.31-1.37(6H, m), 1.41(9H, s), 1.61-1.71(4H, m), 2.73(2H, m), 4.10-4.18(4H, m), 4.84 (1H, br), 5.02(2H, s), 5.06-5.15 (1H, m), 6.01-6.19 (1H, m), 6.87(1H, dd, J=1.2, 9.7Hz), 6.91-6.94(2H, m), 7.12-7.16 (2H, m), 7.22(1H, t, J=7.9Hz), 7.30-7.39(6H, m).

E-form : Example 256

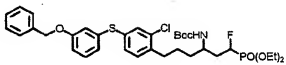
FABMS: 678 ([M+H]+).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.32-1.37(6H, m), 1.43(9H, s), 1.61-1.66(4H, m), 2.72(2H, t, J=7.3Hz), 4.11-4.17(4H, m), 4.50-4.60(2H, m), 5.02(2H, s), 5.73-5.90(1H, m), 6.86-6.89(1H, m), 6.92-6.96(2H, m), 7.10(1H, d, J=7.9Hz), 7.13(1H, dd, J=1.2, 7.9Hz), 7.23(1H, t, J=7.9Hz), 7.31-7.40(6H, m).

<Example 257>

Diethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-1-fluorohexylphosphonate

[0297]



[0298] Using the compounds of Examples 255 and 256, the reaction was carried out in the same manner as in Reference Example 123 to obtain the desired product as a yellow oil.

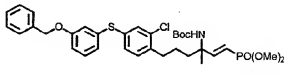
FABMS: 679([M+H]+).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.35 (6H, s), 1.43 (9H, s), 1.49-1.57 (2H, m), 1.58-1.75(4H, m), 2.65-2.80(2H, m), 3.82-3.94 (1H, m), 4.20 (4H, q, J=7.3Hz), 4.35-4.55(1H, m), 4.74-4.94(1H, m), 5.02(2H, s), 6.87-6.99(1H, m), 6.92-6.95(2H, m), 7.11-7.17(2H, m), 7.23(1H, t, J=7.9Hz), 7.32-7.43(6H, m).

<Example 258>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methyl-1-hexenylphosphonate

[0299]

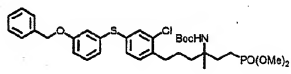


[0300] Following the same procedure as in Example 229, the compound of Example 226 was reacted to form a Boc product and, following the same procedure as in Example 193, the product was oxidized to an aldehyde. Subsequently, using methyl methylenebisphosphonate the same procedure was followed as in Example 232 to give the desired product as a pale yellow oil.
FABMS: 648 ($[M+H]^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.36(3H, s), 1.40(9H, s), 1.54-1.64(2H, m), 1.67-1.70(1H, m), 1.82-1.92(1H, m), 2.69(2H, t, J=7.9Hz), 3.72(6H, d, J=11.0Hz), 4.55(1H, br), 5.02(2H, s), 5.62(1H, dd, J=17.1, 18.3Hz), 6.75(1H, dd, J=17.1, 22.6Hz), 6.80-6.89(1H, m), 6.93-6.96(2H, m), 7.10(1H, d, J=7.9Hz), 7.15(1H, dd, J=1.8, 7.9Hz), 7.23(1H, t, J=7.9Hz), 7.31-7.41(6H, m).

<Example 259>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methylhexylphosphonate

[0301]

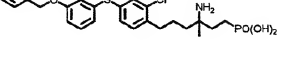


[0302] The compound of Example 258 was reacted in the same manner as in Reference Example 123 to obtain the desired product as a pale yellow oil.
FABMS: 648($[M+H]^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.13(3H, s), 1.41(9H, s), 1.50-1.60(2H, m), 1.65-1.86(4H, m), 2.02-2.08 (2H, m), 2.68(2H, t, J=7.3Hz), 3.73(6H, d, J=11.0Hz), 4.32 (1H, br), 5.01(2H, s), 6.87 (1H, dd, J=2.4, 8.5Hz), 6.91-6.95(2H, m), 7.11 (1H, d, J=7.9Hz), 7.14 (1H, dd, J=1.8, 7.9Hz), 7.22(1H, t, J=7.9Hz), 7.31-7.40(6H, m).

<Example 260>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-methylhexylphophonic acid

[0303]

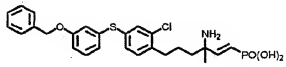


[0304] The compound of Example 259 was reacted in the same manner as in Reference Example 236 to obtain the desired product as a colorless powder.
FABMS: 520([M+H]+).
^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.16 (3H, s), 1.20 (2H, br), 1.53-1.60(6H, m), 1.73(2H, t, J=7.3HZ), 2.65-2.70(2H, m), 5.07(2H, s), 6.89(1H, d, J=7.4Hz), 6.94-6.98(2H, m), 7.21-7.22(1H, m), 7.31-7.37(8H, m).
m.p. = 195-197°C.

<Example 261>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-methyl-1-hexenylphosphonic acid

[0305]



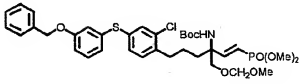
[0306] The compound of Example 258 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 518([M+H]+).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.25(3H, s), 1.39-1.57(2H, m), 1.65-1.79(2H, m), 2.52-2.70(2H, m), 5.05(2H, s), 5.77-5.94(1H, m), 6.08-6.26(1H, m), 6.85(1H, d, J=6.7Hz), 6.91-6.99(2H, m), 7.10-7.42(9H, m), 8.39-9.20(2H, br).
m.p. = 243-245°C.

Elemental analysis (%) : $C_{26}H_{29}ClFNO_4PS{\cdot}H_2O$			
	C	H	N
Calcd	58.26	5.83	2.61
Found	57.80	5.31	2.74

<Example 262>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methoxymethyloxymethyl-1-hexenylphosphonate

[0307]

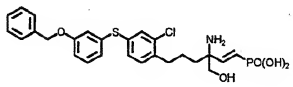


[0308] The compound of Example 222 was reacted in the same manner as in Example 232 to obtain the desired product as a colorless oil.
FABMS: 706([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(9H, s), 1.56-1.69(2H, m), 1.75-1.90(1H, m), 1.93-1.99(1H, m), 2.69(2H, t, J=7.9Hz), 3.33(3H, s), 3.60-3.63(2H, m), 3.71(6H, d, J=11.0Hz), 4.58(2H, s), 4.88 (1H, br), 5.02(2H, s), 5.70 (1H, dd, J=17.7, 18.4Hz), 6.75 (1H, dd, J=17.7, 23.2Hz), 6.87(1H, dd, J=2.4, 9.2Hz), 6.92-6.96(2H, m), 7.10(1H, d, J=7.9), 7.14(1H, dd, J=1.8, 7.9Hz), 7.23(1H, t, J=7.9Hz), 7.30-7.41(6H, m).

<Example 263>

3-amino-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethyl-1-hexenylphosphonic acid

[0309]



[0310] The compound of Example 262 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder

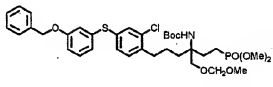
FABMS: 534 ([M+H]$^+$).

^{1}H-NMR(400MHz, DMSOd_6) δ 1.46-1.74(4H. m), 2.57-2.61(2H. m), 3.47-3.52(2H. m), 5.07(2H, s), 5.87-5.96(1H. m), 6.03-6.16(1H, m), 6.87(1H, d, J=7.3Hz), 6.95-6.97(2H. m), 7.19(1H, d, J=9.0Hz), 7.27-7.39(8H, m), 7.81-8.83(2H. br). m.p. =243-246°C.

<Example 264>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methoxymethyloxymethylhexylphosphonate

[0311]



[0312] The compound of Example 262 was reacted in the same manner as in Reference Example 123 to obtain the desired product as a colorless powder.

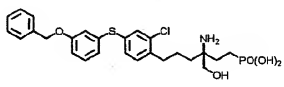
FABMS: 708([M+H]$^+$).

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.41(9H, s), 1.51-1.67(2H, m), 1.70-2.05(6H, m), 2.68 (2H, t, J=7.9Hz), 3.33(3H, s), 3.47-3.53(2H, m), 3.73(6H, d, J=11.0Hz), 4.58(2H, s), 4.61(1H. br), 5.02(2H, s), 6.88 (1H, dd, J=1.8, 7.9Hz), 6.92-6.96 (2H, m), 7.11 (1H, d, J=7.9Hz), 7.14 (1H, dd, J=1.8, 7.9Hz), 7.23(1H, t, J=7.9Hz), 7.30-7.41(6H. m).

<Example 265>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylhexylphosphonic acid

[0313]



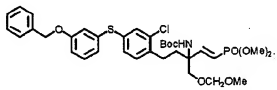
[0314] The compound of Example 264 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 536([M+H]$^+$).
^{1}H-NMR(400MHz, DMSOd_6) δ 1.36-1.73(8H, m), 2.60-2.68(2H, m), 3.31-3.40(2H, m), 5.07(2H. s), 6.88(1H, d, J=7.9Hz), 6.96-6.98(2H, m), 7.20-7.40(9H, m), 7.94-8.94(2H, br).
m.p. = 193-196°C.

Elemental analysis (%) :$C_{26}H_{31}ClNO_5PS{\cdot}1H_2O$			
	C	H	N
Calcd	56.36	6.00	2.53
Found	56.18	5.61	2.51

<Example 266>

Dimethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methoxymethyloxymethyl-1-pentenylphosphonate

[0315]

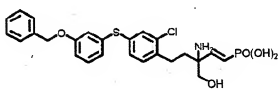


[0316] Following the same procedure as in Example 193, the compound of Example 219 was oxidized and, following the same procedure as in Example 232, the product was reacted with methyl methylenebisphosphonate to obtain the desired product as a colorless oil.
FABMS: 692 ([M+H]$^+$).
^{1}H-NMR(400MHz, CDCl$_3$) δ 1.45(9H, s), 2.10-2.17(2H, m), 2.66-2.73(2H, m), 3.36(3H, s), 3.67-3.78(2H, m), 3.73(6H, d, J=,11.0Hz), 4.63(2H, s), 4.80-4.85(1H, br), 5.02(2H, s), 5.78(1H, dd, J=17.8, 18.3Hz), 6.82(1H, dd, J=17.8, 24.2Hz), 6.87-6.95(3H, m), 7.12-7.13(2H, m), 7.23(1H, t, J=7.9Hz), 7.30-7.41(6H, m).

<Example 267>

3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethyl-1-pentenylphosphonic acid

[0317]

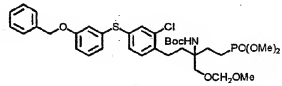


[0318] The compound of Example 266 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 520([M+H]$^+$).
^{1}H-NMR(400MHz, DMSOd_6) δ 1.76-1. 98 (2H. br), 2.50-2.72 (2H. br), 3.47-3.70(3H, m), 5.05(2H. s), 6.03-6.11(1H. m), 6.21-6.33(1H, m), 6.85(1H, d, J=7.4Hz), 6.94(2H, m). 7.15-7.36(9H, m). 8.74(2H, br s).
m.p. = 245-248°C.

<Example 268>

Dimethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-methoxymethyloxymethylpentylphosphonate

[0319]

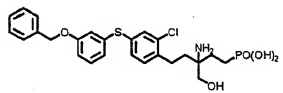


[0320] The compound of Example 266 was reacted in the same manner as in Reference Example 123 to obtain the desired product as a colorless oil.
FABMS: 694([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 1.54-1.60(2H, m), 1.82-1.87(2H, m), 1.98-2.05(2H, m), 2.67-2.70(2H, m), 3.39(3H, s), 3.58-3.64(2H, m), 3.74(6H, d, J=11.0Hz), 4.64(2H, s), 4.74(1H, br), 5.02(2H, s), 6.87(1H, dd, J=1.8, 7.9Hz), 6.91-6.95(2H, m), 7.10-7.15(2H, m), 7.23(1H, t, J=7.9Hz), 7.31-7.41(6H, m).

<Example 269>

3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylpentylphosphonic acid

[0321]



[0322] The compound of Example 268 was reacted in the same manner as in Example 236 to obtain the desired product as a colorless oil.
FABMS: 522 ([M+H]+).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.45-1.58(2H, m), 1.69-1.91(4H, m), 2.58-2.72(2H,m), 3.10-3.75(2H, br), 5.07(2H, s), 6.88(1H, d, J=7.3Hz), 6.96-6.99(2H, m), 7.21(1H, d, J=7.9Hz), 7.27-7.40(8H, m), 7.93-9.02(2H, br).
m.p. = 205-208°C.

Elemental analysis (%) : $C_{25}H_{29}ClNO_5PS \cdot H_2O$			
	C	H	N
Calcd	55.60	5.79	2.59
Found	55.21	5.40	2.68

<Example 270>

(+)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonate monoester ((+)-Example 237)

[0323] Example 245 (250mg) was dissolved in a 10% hydrochloric acid-methanol solution (10mL) and the mixture was allowed to stand overnight. Subsequently, the solvent was removed by distillation and the residue was dissolved

in ethyl acetate, followed by addition of triethylamine to adjust the pH to 7. The crystallized triethylamine hydrochloride was separated by filtration and was washed with ethyl acetate. The solvent was removed by distillation to give a Boc-free product as a colorless oil (250mg). This product was dissolved in acetonitrile (5mL) while the solution was chilled in an ice bath. To this solution, trimethylsilyl iodide (26.7μL) was added and the mixture was stirred for 30min at the same temperature. Subsequently, the solvent was removed by distillation and the residue was purified on a silica gel column chromatography (reversed phase silica chromatography, water : acetonitrile = 9 : 1 to 6 : 1 to 3 : 1 to 1 : 1 to only acetonitrile) to give the desired product as a colorless powder (97mg).
$[\alpha]_D^{25°C}$ =+2.77(C =1.00, DMSO)
FABMS: 524 ([M+H]$^+$).
^{1}H-NMR(400MHz, DMSO+TFA) δ 1.78-1.85(2H, m), 2.78-2.80(2H, m), 3.56(1H, d, J=11.0Hz), 3.61 (1H, d, J=11.0Hz), 3.97(2H, d, J=5.5Hz), 5.08(2H, s), 6.87-6.98 (3H, m), 7.20-7.38(9H, m).

Elemental analysis (%) : $C_{24}H_{27}ClNO_6PS \cdot H_2O$			
	C	H	N
Calcd	53.56	5.25	2.60
Found	53.21	5.25	2.41

<Example 271>

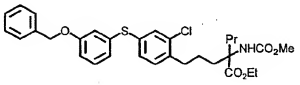
(-)-2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonic acid monoester ((-)-Example 237)

[0324] Using the compound of Example 246, the reaction was carried out in the same manner as in Example 270 to obtain the desired product as a colorless powder.
$[\alpha]_D^{25°C}$ = -2.61 (c =1.00, DMSO).
FABMS: 524 ([M+H]$^+$).
^{1}H-NMR(400MHz, DMSO+TFA) δ 1.76-1.85(2H, m), 2.68-2.78(2H, m), 3.57 (1H, d, J=11.Hz), 3.60 (1H, d, J=11.Hz), 3.97(2H, d, J=5.5Hz), 5.08(2H, s), 6.87-6.98(3H, m), 7.20-7.38(9H, m).

<Example 272>

Ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-propylpentanoate

[0325]

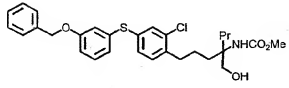


[0326] Using diethyl propylmalonate, the compound of Reference Example 252 was reacted in the same manner as in Example 194 to obtain ethyl 5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethoxycarbonyl-2-propylpentanoate as a yellow oil. This product was hydrolyzed as in Example 198 to obtain a half ester. The half ester was treated in the same manner as in Example 202 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.87(3H, t, J=7.3Hz), 0.89-1.02 (1H, m), 1.24(3H, t, J=7.3Hz), 1.23-1.33(2H, m), 1.52-1.78 (3H. m), 2.24-2..40(2H, m), 2.63-2.68(2H, m), 3.62(3H, s), 4.17-4.22(2H, m), 5.02(2H, s), 5.79(1H, br s), 6.85-6 94 (3H. m), 7.09(1H, d, J=7.9Hz), 7.14 (1H, dd, J=1 8, 7.9Hz), 7.22 (1H, t, J=7 9Hz), 7.29-7.43(6H, m).

<Example 273>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methoxycarbonylamino-2-propylpentane-1-ol

[0327]

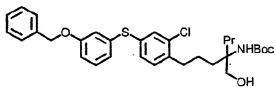


[0328] Using the compound of Example 272, the reaction was carried out in the same manner as in Example 76 to obtain the desired product as a colorless oil.
FABMS: 528([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.3Hz), 1.15-1.35 (2H, m), 1.48-1.69(6H, m), 2.69(2H, t, J=7.3Hz), 3.62(3H, s), 3.70(2H, s), 4.71(1H, br s), 5.01(2H, s), 6.85-6.94(3H, m), 7.12-7.24(3H, m), 7.31-7.40(6H, m).

<Example 274>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-propylpentane-1-ol

[0329]



[0330] Using the compound of Example 273, the reaction was carried out in the same manner as in Example 226 to synthesize 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-propylpentane-1-ol. As in Example 229, the product was reacted to form a Boc product, thereby obtaining the desired compound as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.90(3H, t, J=7.3Hz), 1.15-1.35 (2H, m), 1.42(9H, s), 1.48-1.73(6H, m), 2.70(2H, t, J=7.3Hz), 3.63-3.66(2H, m), 4.51(1H, br s), 5.02(2H, s), 6.86-6.95(3H, m), 7.12-7.24(3H, m), 7.33-7.41(6H, m).

<Examples 275 and 276>

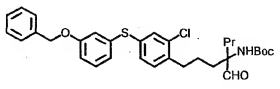
(+) and (-)-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-propylpentane-1-ols

[0331] The compound of Example 274 was optically resolved by HPLC(chiralpak OD-H, hexane : ethanol = 97 : 3, detection wavelength = UV 254nm, flow rate = 3mL/min). The desired products were obtained from the first eluate (Example 275) and the second eluate (Example 276), respectively, each as a colorless oil.
Example 275 $[\alpha]^{25}_D$ -10.2° (C = 1.08, $CHCl_3$) ;
Example 276 $[\alpha]^{25}_D$ +9.48°(C = 1.16, $CHCl_3$).

<Example 277>

5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-t-butoxycarbonylamino-2-propylpentanal

[0332]

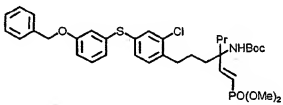


[0333] Using the compound of Example 274, the reaction was carried out in the same manner as in Example 193 to obtain the desired product as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 0.88(3H, t, J=7.3Hz), 1.03-1.37(2H, m), 1.42 (9H, s), 1.48-1.77 (4H, m), 2.02-2.25 (2H, m), 2.65-2.70(2H, m), 5.02(2H, s), 5.27 (1H, br s), 6.86-6.94(3H, m), 7.07-7.14(2H, m), 7.23(1H, t, J=7.8Hz), 7.30-7.41 (6H, m), 9.23(1H, s).

<Example 278>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-propyl-1-hexenylphosphonate

[0334]

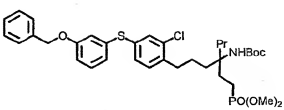


[0335] As in Example 232, the compound of Example 277 was reacted with methyl methylenebisphosphonate to obtain the desired product as a colorless oil.
FABMS: 674 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.88(3H, t, J=7.3Hz), 1.17-1.23(2H, m), 1.40(9H, m), 1.51-1.87(6H, m), 2.58(2H, t, J=7.9Hz), 3.69(3H, d, J=11.0Hz), 3.70 (1H, d, J=11.0Hz), 4.47 (1H, br), 5.02 (2H, s), 5.59 (1H, t, J=17.7Hz), 6.65 (1H, dd, J=23.3, 17.1Hz), 6.86-6.89(3H, m), 7.09-7.15(2H, m), 7.23(1H, t, J=7.9Hz), 7.31-7.41(6H, m).

<Example 279>

Dimethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-propylhexylphosphonate

[0336]



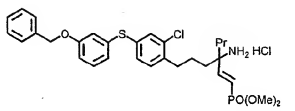
[0337] Using the compound of Example 278, the reaction was carried out in the same manner as in Reference

Example 123 to obtain the desired product as a colorless oil.
FABMS: 676 ([M+H]$^+$)
^{1}H-NMR (400MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.3Hz), 1.15-1.28(2H, m), 1.40(9H, m), 1.51-2.02(10H, m), 2.67(2H, t, J=7.9Hz), 3.72(6H, d, J=11.0Hz), 4.13(1H, br), 5.02(2H, s), 6.87-6.95(3H, m), 7.10-7.25(3H, m), 7.32-7.39(6H, m).

<Example 280>

Dimethyl 3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-propyl-1-hexenylphosphonate hydrochloride

[0338]



[0339] Using the compound of Example 278, the reaction was carried out in the same manner as in Example 233 to obtain the desired product as a colorless oil.
FABMS: 574 ([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSO-d_6$) δ 0.85(3H, t, J=7.3Hz), 1.15-1.28(2H, m), 1.53-1.76(6H, m), 2.66(2H, t, J=7.9Hz), 3.59 (3H, d, J=11.0Hz), 3.62(3H, d, J=11.0Hz), 5.08(2H, s), 6.00(1H, t, J=17.7Hz), 6.57(1H, dd, J=23.8, 17.7Hz), 6.89-7.00 (3H, m), 7.22-7.41(9H, m), 8.47(3H, br s).

<Examples 281 and 282>

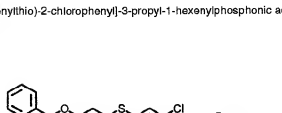
Dimethyl (+)- and (-)-3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-propyl-1-hexenylphosphonate hydrochlorides

[0340] Using the compound of Example 275, the same procedures as in Examples 277, 278 and 280 were sequentially followed to obtain the desired product as a pale yellow amorphous compound ($[\alpha]^{28.2}_D$ +2.9°(C = 1.0, MeOH)) (Example 281). Furthermore, using the compound of Example 276, the same procedure was followed as in Example 281 to obtain the desired product as a pale yellow amorphous compound ($[\alpha]^{28.1}_D$ -1.9°(C = 1.0, MeOH)) (Example 282).

<Example 283>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-propyl-1-hexenylphosphonic acid

[0341]



[0342] Using the compound of Example 278, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 546([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSO-d_6$) δ 0.85(3H, t, J=7.3Hz), 1.19-1.21(2H, m), 1.51-1.69(6H, m), 2.67(2H, t, J=7.9Hz), 5.08

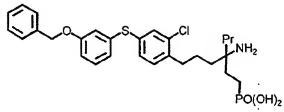
(2H. s), 5.87(1H, dd, J=17.7, 15,2Hz), 6.32(1H, dd, J=23.8, 17.7Hz), 6.88-7.00(3H, m), 7.22-7.41(9H, m).

Elemental analysis (%) : $C_{28}H_{33}ClNO_4PS\cdot 2/3H_2O$			
	C	H	N
Calcd	60.26	6.20	2.51
Found	60.11	5.91	2.32

<Example 284>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-propylhexylphosphonic acid

[0343]



[0344] Using the compound of Example 279, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 548([M+H]$^+$).
^{1}H-NMR(400MHz, DMSOd_6) δ 0.85(3H, t, J=7.3Hz), 1.18-1.21(2H, m), 1.42-1.54 (8H, m), 1.68-1.74 (2H, m), 2.67(2H, br s), 5.08(2H, s), 6.88-7.00(3H, m), 7.22-7.41(9H, m).

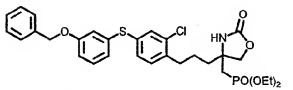
Elemental analysis (%) : $C_{28}H_{35}ClNO_4PS\cdot H_2O$			
	C	H	N
Calcd	59.41	6.59	1.83
Found	59.05	6.14	2.29

m.p. = 197-199°C.

<Example 285>

4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-4-ethoxyphosphorylmethyl-2-oxazolidinone

[0345]



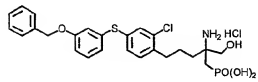
[0346] The compound of Example 188 (330mg) was dissolved in triethyl phosphite (120μL) and the solution was refluxed for 3 hours. Subsequently, the reaction mixture was purified on a silica gel column chromatography (hexane : ethyl acetate = 1 : 1 to 1 : 5) to give the desired product as a pale yellow oil (320mg).
FABMS: 604 ([M+H]$^+$)
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.31-1.35 (6H, m), 1.59-1.72(2H, m), 1.84-1.88(2H, m), 2.10(1H. d, J=19.0Hz), 2.11(1H,

d, J=19.0Hz), 2.74(2H, t, J=7.3Hz), 4.06-4.14(5H, m), 4.17-4.20(1H, m), 5.03(2H, s), 5.89(1H, br s), 6.88 (1H, dd, J=1.2, 7.3Hz), 6.94-6.97 (2H, m), 7.10(1H, d, J=7.9Hz), 7.14(1H, dd, J=1.8, 7.9Hz), 7.24(1H, t, J=7.9Hz), 7.31-7.41 (6H, m).

<Example 286>

2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylpentylphosphonate hydrochloride

[0347]



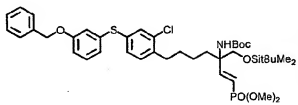
[0348] The compound of Example 285 was reacted in the same manner as in Example 190 and the resulting compound was reacted in the same manner as in Example 233 to obtain the desired product as a colorless powder.
FABMS: 522([M+H]+).
^{1}H-NMR (400MHz, DMSOd_6) δ 1.54-1.62(2H, m), 1.72-1.78(2H, m), 2.64-2.66(2H, m), 3.20-3.31(2H, m), 3.43-3.52 (2H, m), 5.08(2H, s), 6.88-6.90(1H, m), 6.94-7.00(2H, m), 7.21-7.24(1H, dd, J=2.5, 7.9Hz), 7.29-7.41(8H, m).
m.p. = 98-101°C.

Elemental analysis (%) : $C_{25}H_{29}ClNO_5PS$·HCl			
	C	H	N
Calcd	53.77	5.41	2.51
Found	54.18	5.29	2.49

<Example 287>

Dimethyl 7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-t-butyldimethylsiloxymethyl-1-heptenylphosphonate

[0349]

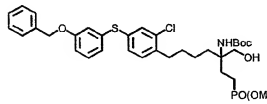


[0350] The compound of Example 130 was reacted with t-$BuMe_2SiCl$ in the same manner as in Example 191. The resulting silyl product was oxidized in the same manner as in Example 193 to obtain an aldehyde. Subsequently, this aldehyde was reacted with methyl methylenebisphosphonate in the same manner as in Example 232 to obtain the desired product as a pale yellow oil.
FABMS: 790([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.04(6H, s), 0.89(9H, s), 1.30-1.37(2H, m), 1.41(9H, s), 1.50-1.60(2H, m), 1.75-1.85(2H, m), 2.68(2H, t, J=7.3Hz), 3.64-3.70(2H, m), 3.71(6H, d, J=11.6Hz), 4.77(1H, br s), 5.02(2H, s), 5.67(1H, dd, J=17.1, 18.3Hz), 6.72(1H, dd, J=17.1, 22.6Hz), 6.67-6.88(1H, m), 6.91-6.94(2H, m), 7.11(1H, d, J=7.9Hz), 7.14 (1H, dd, J=1.8, 7.9Hz), 7.22 (1H, t, J=7.9Hz), 7.31-7.39(6H, m).

<Example 288>

Dimethyl 7-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-hydroxymethylheptylphosphonate

[0351]



[0352] The compound of Example 287 was reduced in the same manner as in Reference Example 123 and the resulting compound (107mg) was dissolved in tetrahydrofuran (5.0mL). A1mol/L TBAF-tetrahydrofuran solution (160μL) was added dropwise and the mixture was stirred for 3 hours at room temperature. Subsequently, water was added and the reaction mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (ethyl acetate only) to obtain the desired product as a colorless oil (47mg).

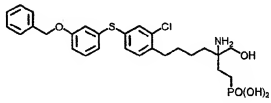
FABMS: 678([M+H]$^+$).

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.42(9H, s), 1.25-1.38(6H, s), 1.70-1.80(2H, m), 1.83-1.95(2H, m), 2.70(2H, t, J=7.9Hz), 3.62(2H, br s), 3.75(6H, d, J=11.0Hz), 4.63(1H, br s), 5.02(2H, s), 6.86-6.89(1H, m), 6.92-6.94(2H, m), 7.10-7.16(2H, m), 7.21-7.23 (1H, m), 7.30-7.40(6H, m).

<Example 289>

3-amino-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylheptylphosphonic acid

[0353]



[0354] Using the compound of Example 288, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless powder.

FABMS: 550([M+H]$^+$).

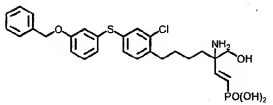
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.22-1.32(2H, m), 1.48-1.60(6H, m), 1.68-1.76(2H, m), 2.64-2.68(2H, m), 3.39-3.50(2H, m), 5.08(2H, s), 6.88-6.90 (1H, m), 6.95-6.99(2H, m), 7.20 (1H, dd, J=1.9, 9.8Hz), 7.28-7.40(8H, m).

m.p. = 180-183°C.

<Example 290>

3-amino-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethyl-1-heptenylphosphonic acid

[0355]

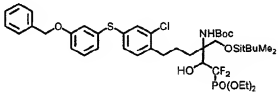


[0356] Following the same procedure as in Example 244, the compound of Example 287 was desilylated and the resulting product was reacted in the same manner as in Example 236 to obtain the desired product as a colorless powder.
FABMS: 548([M+H]+).
^{1}H-NMR (400MHz. DMSOd_6) δ 1.27-1.38(2H, m), 1.43-1.52(2H, m), 1.61-1.72(2H, m), 2.53-2.66(2H, m), 3.46-3.58 (2H, m), 5.02(2H, s), 5.88-5.97(1H, m), 6.06-6.17(1H, m), 6.85-6.87(1H, m), 6.94-6.96(2H, m), 7.15-7.17(1H, m), 7.26-7.38(8H, m).
m.p. = 258-260°C.

<Example 291>

Diethyl 6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-t-butoxycarbonylamino-3-t-butyldimethylsilyloxy-1,1-difluoro-2-hydroxyhexylphosphonate

[0357]

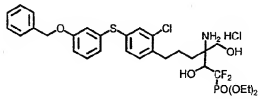


[0358] The compound of Example 128 was reacted with t-BuMe_2SiCl in the same manner as in Example 191. The resulting silyl product was oxidized in the same manner as in Example 193 to obtain an aldehyde. This aldehyde was reacted as follows: a 1.58mol/L-LDA-tetrahydrofuran solution (1.50mL) was added to a tetrahydrofuran solution (9mL) while the mixture was kept at - 78°C. To the resulting mixture, diethyl difluoromethylphosphonate (372μL) was added dropwise over 15min and the mixture was stirred for 20min. To this mixture, the aldehyde (490mg) in tetrahydrofuran (1.0mL) was added dropwise over 20min while the internal temperature was kept at -73°C or below. Subsequently, the mixture was stirred for 1.5 hours. A saturated aqueous solution of ammonium chloride was then added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the resulting residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to obtain the desired product as a colorless oil (439mg).
FABMS: 858([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.06(6H, s), 0.88(9H, s), 1.33-1.40(6H, m), 1.46(9H, s), 1.56-1.70(4H, m), 2.69(2H, t, J=7.3Hz), 3.82-3.84(1H, m), 4.23-4.33(6H, m), 5.02(2H, s), 5.05(1H, br s), 6.85-6.88(1H, m), 6.91-6.95(2H, m). 7.12-7.14(2H, m), 7.22(1H, t, J=7.9Hz), 7.31-7.40(6H, m).

<Example 292>

Diethyl 3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1,1-difluoro-2-hydroxy-3-hydroxymethylhexylphosphonate hydrochloride

[0359]

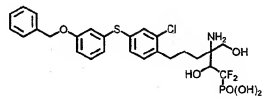


[0360] Following the same procedure as in Example 244, the compound of Example 291 was desilylated and the resulting product was reacted in the same manner as in Example 233 to obtain the desired product as a colorless amorphous product.
FABMS: 644 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.22-1.27(6H, m), 1.55-1.79(4H, m), 2.62-2.65(2H, m), 3.59-3.73(2H, m), 4.04-4.11(4H, m), 4.68-4.90 (1H, m), 5.09(2H, s), 6.88-6.90(1H, m), 6.94-7.00(2H, m), 7.22-7.25 (1H, m), 7.29-7.41(8H, m).

<Example 293>

3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-1,1-difluoro-2-hydroxy-3-hydroxymethylhexylphosphonic acid

[0361]

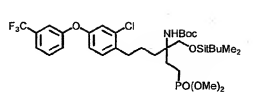


[0362] Using the compound of Example 292, the reaction was carried out in the same manner as in Example 238 to obtain the desired product as a colorless amorphous product.
FABMS: 588([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.55-1.86(4H, m), 2.55-2.65(2H, m), 3.51-3.67(4H, m), 3.78-3.84(1H, m), 5.08(2H, s), 6.88(1H, d, J=7.9Hz), 6.90-7.00(2H, m), 7.20-7.23(1H, m), 7.29-7.41(8H, m).

<Example 294>

Dimethyl 3-t-butoxycarbonylamino-3-t-butyldimethylsiloxymethyl-6-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl] hexylphosphonate

[0363]



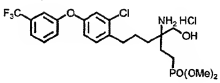
[0364] The compound of Example 149 was reacted with t-BuMe$_2$SiCl in the same manner as in Example 191. The resulting silyl product was oxidized in the same manner as in Example 193 to obtain an aldehyde. Subsequently, following the same procedure as in Example 232, this aldehyde was condensed with methyl methylenebisphosphonate and, following the same procedure as in Reference Example 123, the resulting product was reduced to give the desired product as a colorless oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 0.04(6H, s), 0.88(9H, s), 1.42(9H, s), 1.56-1.64(4H, m), 1.64-1.77(2H, m), 1.90-1.97.(2H, m), 2.69(2H, t, J=7.3Hz), 3.49-3.58(2H. m). 3.73(6H, d, J=11.0Hz), 4.47(1H, br s), 6.85(1H, dd. J=2.5, 8.6Hz), 7.01 (1H. d, J=2.5Hz), 7.14-7.18(2H. m). 7.25-7.26(1H, m), 7.36(1H, t, J=7.9Hz). 7.45(1H, t. J=7.9Hz).

<Example 295>

Dimethyl 3-amino-6-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl]-3-hydroxymethylhexylphosphonate hydrochloride

[0365]



[0366] Following the same procedure as in Example 244, the compound of Example 294 was desilylated and the resulting product was reacted in the same manner as in Example 233 to obtain the desired product as a colorless amorphous product.

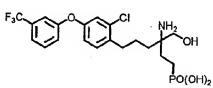
FABMS: 510 ([M+H]$^+$) .

^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.54-1.64(4H, m), 1.67-1.80(4H, m), 2.65-2.69(2H, m), 3.40-3.41(2H, m), 3.68(6H. d, J=10.4Hz), 5.51(1H, br s), 7.03(1H, dd, J=2.4, 8.6Hz), 7.20(1H, d, J=2.4Hz), 7.28-7.29(1H, m), 7.35(1H, s), 7.39(1H, d, J=7.9Hz), 7.51(1H, d, J=7.9Hz), 7.63(1H. t, J=7.9Hz), 7.91(3H, br s).

<Example 296>

3-amino-6-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl]-3-hydroxymethylhexylphosphonic acid

[0367]



[0368] Using the compound of Example 295, the reaction was carried out in the same manner as in Example 236 to obtain the desired product as a colorless amorphous product.

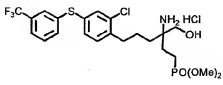
FABMS: 482 ([M+H]$^+$).

^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.48-1.60 (6H, m). 1.60-1.75 (2H. m), 2.60-2.67 (2H, m). 3.40(2H. s). 7.01 (1H, dd, J=2.4, 7.9Hz), 7.15-7.19(1H, m). 7.28(1H, d, J=7.9Hz), 7.35(1H, s), 7.39(1H, d, J=7.9Hz), 7.50(1H, d, J=7.9Hz). 7.62 (1H. t, J=7.9). 7.77-8.11(3H, br).

<Example 297>

Dimethyl 3-amino-6-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]-3-hydroxymethylhexylphosphonate hydrochloride

[0369]

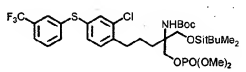


[0370] The compound of Example 76 was reacted in the same manner as in Example 294 and the resulting compound was reacted in the same manner as in Example 295 to obtain the desired product as a colorless oil.
FABMS: 525([M+H]+).
^{1}H-NMR(400MHz, DMSOd_6) δ 1.46-1.62(4H, m), 1.62-1.83(4H, m), 2.64-2.66(2H, m), 3.40-3.45(2H, m), 3.61(6H, d, J=10.4Hz), 7.34(1H, dd, J=1.8, 8.0Hz), 7.40-7.42(1H. m), 7.49(1H, dd, J=1.8Hz), 7.54-7.56(1H, m), 7.59-7.62(2H, m), 7.66-7.68(1H, m), 7.86(3H, br s).

<Example 298>

2-t-butoxycarbonylamino-2-t-butyldimethylsiloxymethyl-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]-1-dimethoxyphosphoryloxypentane

[0371]

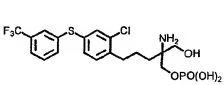


[0372] Following the same procedure as in Example 191, the compound of Example 76 was reacted with t-BuMe_2SiCl and, following the same procedure as in Example 223, the resulting silyl product was reacted to give the desired product as a colorless oil.
FABMS: 741([M+H]+).
^{1}H-NMR(400MHz, $CDCl_3$) δ 0.05(6H, s), 0.87(9H, s), 1.41(9H, s), 1.60-1.91(4H, m), 2.71(2H, t, J=7.9Hz), 3.60(1H, d, J=9.2Hz), 3.64(1H, d, J=9.2Hz), 3.76(6H, d, J=11.0Hz), 4.09-4.15(2H, m), 4.66(1H, br), 7.14-7.20(2H, m), 7.30-7.55(5H, m).

<Example 299>

2-amino-5-[2-chloro-4-(3-trifluoromethylphenylthio)phenyl]-2-hydroxymethylpentylphosphonate monoester

[0373]



[0374] To a tetrahydrofuran solution (20mL) of the compound of Example 298 (1.29g), a 1mol/L TBAF-tetrahydrofuran

solution (2.09mL) was added dropwise and the mixture was stirred for 4 hours at room temperature. Subsequently, water was added and the reaction mixture was extracted with ethyl acetate. The extract was washed sequentially with water and a saturated aqueous solution of sodium chloride and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was purified on a silica gel column chromatography (hexane : ethyl acetate = 1 : 1 to ethyl acetate only) to obtain a desilylated product as a colorless oil (1.00g). The resulting compound (1.00g) was dissolved in a 10% hydrochloric acid-metnanol solution (20mL) and the mixture was left overnight at room temperature. Subsequently, the solvent was removed by distillation and the residue was dissolved in ethyl acetate. The solution was neutralized with triethylamine. The crystallized triethylamine hydrochloride was separated by filtration and the solvent was removed by distillation to give a colorless oil (1.00g). The oil was dissolved in acetonitrile (15mL) while the solution was chilled in en ice bath. To this solution, TMSI (905μL) was added and the mixture was stirred for 60min. The reaction mixture was concentrated and was purified on a silica gel column chromatography (water : acetonitrile = 9 : 1 to 6 : 1 to 3 : 1 to 1 : 1 to acetonitrile only) to obtain the desired product as a colorless powder (384g).

FABMS: 500([M+H]$^+$).

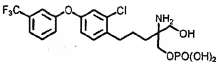
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.60(4H, br s), 2.66(2H, br s), 3.36-3.45(2H, m), 3.68-3.76(2H, m), 7.32(1H, dd, J=1.8, 8.5Hz), 7.38-7.45(2H, m), 7.50-7.56(1H, m), 7.57-7.68(3H, m).

Elemental analysis (%) :$C_{19}H_{22}ClF_5NO_5PS\cdot1/4H_2O$			
	C	H	N
Calcd	45.24	4.50	2.78
Found	45.05	4.31	2.72

<Example 300>

2-amino-5-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl]-2-hydroxymethylpentylphosphonate monoester

[0375]



[0376] The compound of Example 149 was reacted in the same manner as in Example 298 and the resulting compound was reacted in the same manner as in Example 299 to obtain the desired product as a colorless powder.

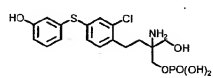
FABMS: 484 ([M+H]$^+$).

^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.61(4H, br), 2.64 (2H, br), 3.41 (1H, d, J=11.6Hz), 3.51(1H, d, J=11.6Hz), 3.69-3.80 (2H, m), 7.00(1H, dd, J=2.5, 8.6Hz), 7.16(1H, d, J=2.5Hz), 7.29(1H, dd, J=2.5, 8.6Hz), 7.35 (1H, s), 7.40 (1H, d, J=8.6Hz), 7.50 (1H, d, J=8.0Hz), 7.61(1H, t, J=8.0Hz).

<Example 301>

2-amino-4-[2-chloro-4-(3-hydroxyphenylthio)phenyl]-2-hydroxymethylbutylphosphonate monoester

[0377]



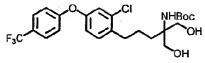
[0378] Using the compound of Example 223, the reaction was carried out in the same manner as in Example 238

to obtain the desired product as a colorless powder.
FABMS: 434 ([M+H]$^+$).
^{1}H-NMR (400MHz, DMSOd_6) δ 1.72-1.92(2H, m), 2.63-2.82(2H, m), 3.48-3.60(2H, m), 3.71-3.90(2H, m), 6.66-6.78 (3H, m), 7.14-7.37(4H, m).

<Example 302>

2-t-butoxycarbonylamino-2-[2-chloro-4-(4-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol

[0379]

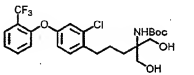


[0380] The compound of Reference Example 323 was reacted in the same manner as in Example 1 and the resulting compound was reduced in the same manner as in Example 76 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44 (9H, s), 1.57-1.74(4H, m), 2.70(2H, t, J=6.7Hz), 3.33(2H, br s), 3.61(2H, d,d, J=6.7, 11.6Hz), 3.84(2H, d,d, J=6.7, 11.6Hz), 4.93(1H, br s), 6.89(1H, dd, J=2.5, 8.0Hz), 6.98-7.07(3H, m), 7.21(1H, d, J=8.6Hz), 7.59(2H, d, J=8.6Hz).

<Example 303>

2-t-butoxycarbonylamino-2-[2-chloro-4-(2-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol

[0381]

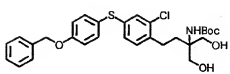


[0382] The compound of Reference Example 324 was reacted in the same manner as in Example 1 and the resulting compound was reduced in the same manner as in Example 76 to obtain the desired product as a colorless powder.
FABMS: 504 ([M+H]$^+$).
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.44(9H, s), 1.58-1.66(4H, m), 2.70(2H, t, J=6.7Hz), 3.35(2H, br s), 3.60(2H, d,d, J=7.3, 11.6Hz), 3.84(2H, d,d, J=7.3, 11.6Hz), 4.92(1H, br s), 6.87(1H, dd, J=2.5, 8.0Hz), 6.96(1H, d, J=8.0Hz), 7.03(1H, d=2.5Hz), 7.15-7.22 (2H, m), 7.48 (1H, t, J=7.3Hz), 7.68 (1H, d, J=6.7Hz).

<Example 304>

2-t-butoxycarbonylamino-2-[4-(4-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol

[0383]

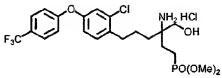


[0384] The compound of Reference Example 327 was reacted in the same manner as in Example 1 and the resulting compound was reduced in the same manner as in Example 76 to obtain the desired product as a colorless oil.
FABMS: 543 ([M+H]$^+$).
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.78-1.84(2H, m), 2.64-2.71(2H, m), 3.23-3.39 (2H, m), 3.65(2H, d.d, J=6.7, 11.6Hz), 3.84(2H, d,d, J=6.7, 11.6Hz), 5.07(1H, s), 5.08(2H. s), 6.96-7.00(3H. m), 7.07-7.13(2H, m), 7.345-7.44(7H, m).

<Example 305>

Dimethyl 3-amino-6-[2-chloro-4-(4-trifluoromethylphenoxy)phenyl]-3-hydroxymethylhexylphosphonate hydrochloride

[0385]

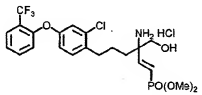


[0386] The compound of Example 302 was treated in the same manner as in Example 294 and the resulting compound was reacted in the same manner as in Example 295 to obtain the desired product as a colorless amorphous product.
FABMS: 510 ([M+H]$^+$).
^{1}H-NMR (400MHz, $DMSOd_6$) δ 1.51-1.60(4H, m), 1.65-1.82(4H, m), 2.68(2H, br s), 3.42(2H, s), 3.61(6H, d, J=11.0Hz), 7.08(1H, dd, J=2.4, 8.6Hz), 7.15(2H, d, J=8.6Hz), 7.26 (1H, d, J=2.4Hz), 7.42(1H, s, 8.6Hz), 7.75(2H, d, 8.6HzHz), 7.89(3H, br s).

<Example 306>

Dimethyl 3-amino-6-[2-chloro-4-(4-trifluoromethylphenoxy)phenyl]-3-hydroxymethyl-1 hexenylphosphonate hydrochloride

[0387]

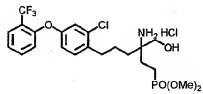


[0388] The compound of Example 303 was reacted in the same manner as in Example 287 and the resulting compound was desilylated in the same manner as in Example 244. The desilylated product was then reacted in the same manner as in Example 233 to obtain the desired product as an amorphous product.
FABMS: 508 ([M+H]$^+$).
^{1}H-NMR(400MHz, $DMSOd_6$) δ 1.42-1.62(2H, m), 1.68-1.82(2H, m), 2.66(2H, t, J=2.7Hz), 3.42 (2H. br s), 3.60(6H, d, J=11.0Hz), 6.00(1H, t, J=17.7Hz), 6.56(1H, dd, J=17.7, 22.6Hz), 6.97(1H, dd, J=2.5, 8.6Hz), 7.11(1H, d, J=8.6 Hz), 7.13 (1H, d=2.5Hz), 7.32-7.40(2H, m), 7.67(1H, t, J=8.0Hz), 7.79(1H, t, J=7.3Hz), 8.22-8.38(3H, br s).

<Example 307>

Dimethyl 3-amino-6-[2-chloro-4-(4-trifluoromethylphenoxy)phenyl]-3-hydroxymethylhexylphosphonate hydrochloride

[0389]

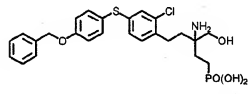


[0390] Using the compound of Example 303, the reaction was carried out in the same manner as in Example 305 to obtain the desired product as a colorless amorphous product
FABMS: 510([M+H]$^+$).
^{1}H-NMR(400MHz, DMSOd_6) δ 1.50-1.60(4H, m), 1.65-1.82(4H, m), 2.60-2.70(2H, m), 3.52-3.55(2H, m), 3.61(6H, d, J=11.0Hz). 6.98(1H, dd, J=2.4, 8.6Hz), 7.08(1H, d, J=8.6Hz), 7.13(1H, d, J =2.4Hz), 7.33-7.41(2H, m), 7.68(1H, t, J=7.3), 7.80 (1H, d, J=7.3Hz), 7.75-7.85(3H, br s).

<Example 308>

3-amino-5-[4-(4-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylpentylphosphonic acid

[0391]

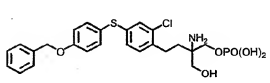


[0392] The compound of Example 304 was reacted in the same manner as in Example 294 and the resulting compound was reacted in the same manner as in Example 290 to obtain the desired product as a colorless powder.
FABMS: 522([M+H]$^+$).
^{1}H-NMR(400MHz, DMSOd_6) δ 1.47-1.62 (2H, m), 1.62-1.91(4H, m), 2.55-2.67(2H, m), 3.40-3.54(2H, m), 5.12(2H, s), 6.98-7.10(4H, m), 7.25-7.51(8H, m).

<Example 309>

2-amino-4-[4-(4-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonate monoester

[0393]



[0394] The compound of Example 304 was reacted in the same manner as in Example 298 and the resulting compound was reacted in the same manner as in Example 299 to obtain the desired product as a colorless powder.

FABMS: 524 ((M+H)+)
^{1}H-NMR(400MHz, $DMSO-d_6$) δ 1.70-1.77 (2H, m), 2.65-2.69(2H, m), 3.49-3.53(2H, m), 3.72-3.86(2H, m), 5.13(2H, s), 7.06-7.10(4H, m), 7.25-7.27(1H, m), 7.33-7.46(7H, m).

[0395] Next, some experiment examples will be described, that demonstrate the efficacy of the compound of the present invention.

<Experiment Example 1> Test for the ability of test compounds to induce intracellular Ca^{2+} mobilization in cells expressing human S1P (sphingosine-1-phosphate) receptors

[0396] CHO cells expressing human S1P receptors (i.e., CHO cells expressing $hS1P_1$ receptors or $hS1P_3$ receptors) were subcultured on Ham's F-12 medium supplemented with 10% fetal bovine serum and 200μg/mL Geneticin. The cells were seeded on a 96-well black clear bottom plate (COSTAR) at $4x10^4$ cells/well and were cultured overnight at 37°C in 5% CO_2. A fluorescent reagent that emits fluorescence upon binding to Ca^{2+} (Calcium Screening Kit (DOJINDO)) was added to the culture and the cells were further cultured for 60min at 37°C in 5% CO_2. After culturing, microplate spectrofluorometer (FLEX station, MOLECULAR DEVICE) was used to measure the fluorescence intensity at an excitation wavelength of 485 nm and a detection wavelength of 525 nm. S1P or a test compound adjusted with cultural medium to a concentration 10 times higher than the final concentration (final DMSO concentration = 0.1%). Each test compound solution was added 18sec. after beginning of the measurement of fluorescence. The fluorescence intensity was measured every 1.5sec for 100sec. For each test compound, the difference between the maximum fluorescence intensity and the minimum fluorescence intensity (*i.e.*, increase in fluorescence) was determined from the measurements. The rate of fluorescence increase (%) for each test compound was calculated by the difference (100%) of the fluorescence increase between solvent only and S1P (10^{-6}M). Using this value as an index of the ability of the test compound to induce intracellular Ca^{2+} mobilization, EC50 was determined by PRISM software (GraphPad). In Table 11, the symbol "-" indicates that the test compound was determined to have an EC50 of 1μmol/L or higher, the symbol "+" indicates that the test compound had an EC50 of lower than 1μmol/L and higher than or equal to 0.1μmol/L, the symbol "++" indicates that the test compound had an EC50 of lower than 0.1μmol/L and higher than or equal to 0.01μmol/L, and the symbol "+++" indicates that the test compound had an EC50 of lower than 0.01μmol/L.

Table 11

Example No.	S1P1	S1P3	Example No.	S1P1	S1P3
236	++	++	265	+++	+
237	+++	+++	267	+++	-
238	+	-	269	++	-
239	+++	+++	280	+	+
240	++	+	283	++	++
241	+	-	284	++	+
242	+	-	286	++	-
249	++	+++	290	+++	++
250	+	-	293	+	+
253	+	+	296	++	-
254	++	-	299	++	-
260	++	+	300	++	-
261	+	-	307	+	-
263	+++	+	308	+	-

[0397] These results indicate that the compounds of the present invention act on human S1P receptors.

<Experiment Example 2> Test for the ability of test compounds to induce activation of extracellular regulatory kinase (ERK) in cells expressing human S1P receptors

[0398] CHO cells expressing human S1P receptors (i.e., CHO cells expressing $hS1P_4$ receptors) were subcultured on Ham's F-12 medium supplemented with 10% fetal bovine serum and 200μg/mL Geneticin. The cells were seeded on a 6-well cell culture plate (COSTAR) at $3x10^5$ cells/well and were cultured overnight at 37°C in 5% CO_2. On the following day, the medium was replaced with FBS-free Ham's F-12 medium (containing 0.1% fatty acid-free bovine serum albumin) and the cells were cultured overnight at 37°C in 5% CO_2. S1P or a test compound adjusted with Ham's

F-12 medium (with 0.1% fatty acid-free bovine serum albumin) to a concentration 10 times higher than the final concentration (final DMSO concentration = 0.1%). Each test compound solution was added to this culture plate. The cells were cultured for 5min at 37°C in 5% CO_2. The medium was removed and the cells were washed with a 200μmol/L ice-cold PBS containing Na_3VO_4. A lysis buffer (20mmol/L Tris-HCl pH7.5, 1% Triton X-100, 1mmol/L EDTA, 1mmol/L EGTA, 0.5mmol/L Na_3VO_4, 0.1% β-mercaptoethanol, 50mmol/L NaF, 5mmol/L $Na_4O_7P_3$, 10mmol/L $C_3H_7O_6Na$, 1μmol/L Microcystin LR, 1×Complete Protease Inhibitor Cocktail (ROCHE)) was then added to the cells and the reaction was carried out on ice for 5min to lyse the cells. The cell lysate was subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) to separate proteins. The proteins were transferred to a PVDF membrane (Hybond-P, Amersham Biosciences). The membrane was reacted overnight at 4°C with anti-phospho ERK (p42/44 MAPK) monoclonal antibody (E10, Cell Signaling Technologies) diluted 1000-fold, and was subsequently reacted for 1 hour at room temperature with alkaline phosphatase-labeled anti-mouse IgG antibody (Molecular Probe) diluted 6000-fold. After washing with 20mmol/L Tris-HCl and 150mmol/L NaCl solution, the PVDF membrane was fluorostained with DDAO phosphate (DyeChrome Western Blot Stain Kit, Molecular Probe), a fluorescent substrate of alkaline phosphatase. The fluorescence was detected using a variable image analyzer (Typhoon 8600, Amersham Biosciences). The detected signal of phosphorylated ERK was quantified using ImageQuant software (Molecular Dynamics). The rate of ERK activation (%) for each test compound was calculated by the difference (100%) of the signal intensity between solvent only and S1P (10^{-6}mol/L). The results are shown in Table 12 below.

Table 12

Example No.	Compound Conc (nmol/L)	Induction effect of ERK activation on hS1P-expressing CHO cells (Activation rate (%) relative to the activated ERK at S1P10-6mol/L)
236	1	8.0
	10	119.5
237	1	35.8
	10	80.7

[0399] These results indicate that the compounds of the present invention induce ERK activation by acting on human S1P receptors.

<Experiment Example 3>

Inhibitory effects of test compounds on host vs. graft rejection in mice

[0400] This experiment was performed according to the method described in *Transplantation* 55(3) (1993): 578-591. Spleens were collected from 6 to 16 week old male BALB/c mice (CHARLES RIVER JAPAN). The spleens were placed in an RPMI-1640 medium (SIGMA) and were gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon) to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The cells were then centrifuged three times in RPMI-1640 medium for washing and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere. The cells were centrifuged three times in RPMI-1640 medium for washing and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 6 to 8 week old male C3H/HeN mice (CLEA JAPAN). Normal control group was injected with RPMI-1640 medium alone. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (i.e., total of 4 times). Control groups were administered the same vehicle as that used in the preparation of each test compound. The results are shown in Table 13 below. The inhibition (%) was determined using the following formula

Formula 1:

{[Weight of right popliteal lymph nodes of positive control group] - [Weight of

right popliteal lymph nodes of test compound group]x100)/([Weight of right popliteal lymph nodes of positive control group]-[Weight of right popliteal lymph nodes of normal control group])

Table 13

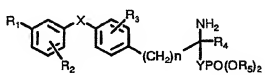
Example No.	Dose (mg/kg)	Inhibition (%)
233	30	53
235	30	56
236	0.03	73
237	0.1	75
238	3	65
239	0.03	65
241	10	46
242	10	62
247	0.03	63

INDUSTRIAL APPLICABILITY

[0401] As set forth, the present invention has been devised in recognition of the fact that the novel aminophosphonic acid derivatives with a diarylsulfide or diarylether group exhibit a strong ability to modulate S1P receptors. Effective modulators of S1P receptors, the compounds of the present invention have a great potential as a prophylactic or therapeutic agent against peripheral vascular diseases, such as arteriosclerosis, arteriosclerosis obliterans, renal fibrosis, hepatic fibrosis, chronic bronchial asthma, diffuse pulmonary hamartoangiomyomatosis, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), interstitial pneumonia, idiopathic interstitial pneumonia, lung cancer, hypersensitivity pneumonitis, Buerger's disease, diabetic neuropathy septicemia, angiitis, nephritis, pneumonia, cerebral infarction, myocardial infarction, edema, varicose veins, dissecting arterial aneurysm, stenocardia, DIC, pleuritis, congestive heart failure, multiple organ failure, bed sore, burn, ulcerative colitis and Crohn's disease. The compounds of the present invention also act as effective prophylactic or therapeutic agents against rejection of heart transplants, kidney transplants, skin grafts, liver transplants and bone marrow transplants, or against rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus, Hashimoto's disease, multiple sclerosis, myasthenia gravis, diabetes, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, allergic contact dermatitis and various other diseases.

Claims

1. An aminophosphonic acid derivative represented by the following general formula (1):

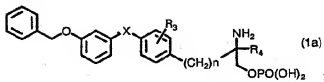


(1)

[wherein R_1 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a hydroxy group, a phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a substituted or unsubstituted phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to

4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group: R_2 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms, an aralkyl group or an aralkyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; R_4 is a hydrogen atom, a halogen atom, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxymethyl group having 1 to 4 carbon atoms, a lower alkylthiomethyl group having 1 to 4 carbon atoms, a hydroxymethyl group, a phenyl group or an aralkyl group: R_5 is a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; Y is $-CH_2O-$, $-CH_2-$, $-CH=CH-$, $-CH=CF-$, $-CH_2CH_2-$, $-CH_2CFH-$, $-CH_2CF_2-$ or $-CH(OH)CF_2-$; and n is an integer from 1 to 4], and an optical isomer, and a pharmaceutically acceptable salt and a hydrate thereof.

2. The 2-aminophosphonic acid monoester derivative according to claim 1, and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof, wherein the compounds represented by the general formula (1) comprise compounds represented by the following general formula (1a):

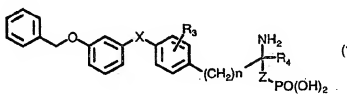


(1a)

[wherein X, R_3, R_4 and n are as defined above].

3. The 2-aminophosphonic acid monoester derivative according to claim 2, and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof, wherein R_3 is a chlorine atom.

4. The 3-aminophosphonic acid derivative according to claim 1, and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof, wherein the compound represented by the general formula (1) comprise compounds represented by the following general formula (1b):



(1b)

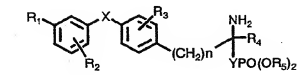
[wherein Z is $-CH_2-$, $-CH=CH-$, $-CH=CF-$, $-CH_2CH_2-$, $-CH_2CHF-$, $-CH_2CF_2-$ or $-CH(OH)CF_2-$; and X, R_3, R_4 and n are as defined above].

5. The 3-aminophosphonic acid derivative according to claim 4, and the optical isomer, and the pharmaceutically acceptable salt and the hydrate thereof, wherein R_3 is a chlorine atom.

6. The aminophosphonic acid ester derivative according to claim 1, and the pharmaceutically acceptable salt and the hydrate thereof, wherein the compound represented by the general formula (1) is

1) 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylpentylphosphonic acid monoester,
2) 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-methylbutylphosphonic acid monoester,
3) 2-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylpentylphosphonic acid monoester,
4) 2-amino-4-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-hydroxymethylbutylphosphonic acid monoester,
5) 3-amino-5-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylpentylphosphonic acid, or
6) 3-amino-6-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-3-hydroxymethylhexylphosphonic acid,

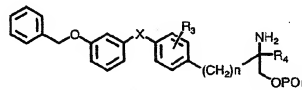
7. An S1P receptor modulator containing as an active ingredient at least one of aminophosphonic acid derivatives represented by the following general formula (1):



(1)

[wherein R_1 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a hydroxy group, a phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a substituted or unsubstituted phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a halogenated or unhalogenated lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms, an aralkyl group or an aralkyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; R_4 is a hydrogen atom, a halogen atom, a lower alkyl group having 1 to 4 carbon atoms, a lower alkoxymethyl group having 1 to 4 carbon atoms, a lower alkylthiomethyl group having 1 to 4 carbon atoms, a hydroxymethyl group, a phenyl group or an aralkyl group; R_5 is a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; Y is $-CH_2O-$, $-CH_2-$, -CH=CH-, -CH=CF-, $-CH_2CH_2-$, $-CH_2CFH-$, $-CH_2CF_2-$ or $-CH(OH)CF_2-$; and n is an integer from 1 to 4], and optical isomers, and pharmaceutically acceptable salts and hydrates thereof.

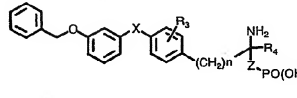
8. The S1P receptor modulator according to claim 7, wherein the compound represented by the general formula (1) contains as an active ingredient at least one of 2-aminophosphonic acid monoester derivatives represented by the following general formula (1a):



(1a)

[wherein R_3, R_4, X and n are as defined above], and the optical isomers, the pharmaceutically acceptable salts and the hydrates thereof.

9. The S1P receptor modulator according to claim 7, wherein the compound represented by the general formula (1) contains as an active ingredient at least one of 2-aminophosphonic acid derivatives represented by the following general formula (1b):



(1b)

[wherein R_3, R_4, X, Z and n are as defined above], and the optical isomers, the pharmaceutically acceptable salts and the hydrates thereof.

10. A pharmaceutical agent containing as an active ingredient at least one of the aminophosphonic acid derivatives according to any one of claims 1 to 9, and the optical isomers, the pharmaceutically acceptable salts and the hydrates thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/001783

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07F9/09, 9/38, 9/40, A61K31/661, 31/662, A61P1/04, 9/00, 9/10, 11/00, 11/06, 13/12, 17/00, 29/00, 37/02, 37/06, 37/08, 43/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07F9/09, 9/38, 9/40, A61K31/661, 31/662, A61P1/04, 9/00, 9/10, 11/00, 11/06, 13/12, 17/00, 29/00, 37/02, 37/06, 37/08, 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/064616 A2 (UNIVERSITY OF VIRGINA PATENT FOUDATION), 22 August, 2002 (22.08.02), & EP 1383778 A2	1-10
A	US 5447922 A (Bristol-Myers Squibb Co.), 05 September, 1995 (05.09.95), & EP 698609 A1 & JP 8-73477 A	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 April, 2004 (06.04.04)	20 April, 2004 (20.04.04)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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